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THE BRITISH JOURNAL OF DISEASES OF THE CHEST
Published in Association with the British Thoracic Association

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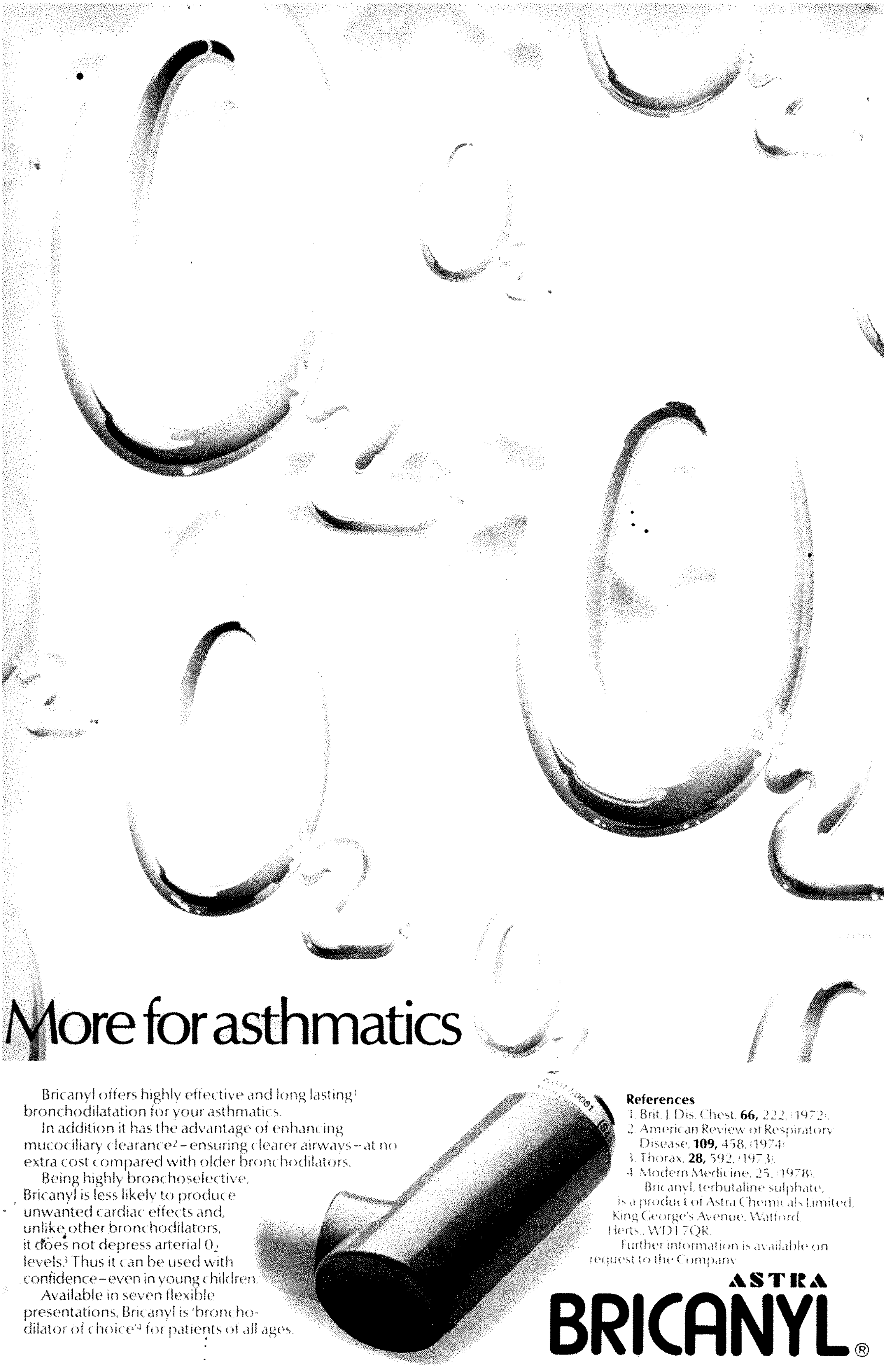

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Historical Review

THE HISTORY OF SPIROMETRY

E. A. Spriggs

Northern Counties Chest Hospital, Newcastle upon Tyne

This paper describes the gropings of medical scientists, mostly in the last three hundred years, towards useful quantitative ventilatory measurements such as are nowadays made in every hospital medical department and many general practices. I have transcribed the uncii (or unciae), pollices, digiti, inches, lineae and pints into metric units, using certain older conversion tables (*Annals of Philosophy* 1813, Faraday 1842) and standard modern ones, and rejoice that the Système Internationale will not necessitate further revision.

It may be stated for the benefit of any reader unfamiliar with respiratory physiology that when a man breathes quietly, and then takes the deepest possible inspiration, and follows this with the deepest possible expiration, a number of useful measurements can be made, particularly the tidal volume and the vital capacity (Fig. 1). There is a lot of normal variation, but the following are characteristic figures for a healthy young man, those for a woman being rather less:

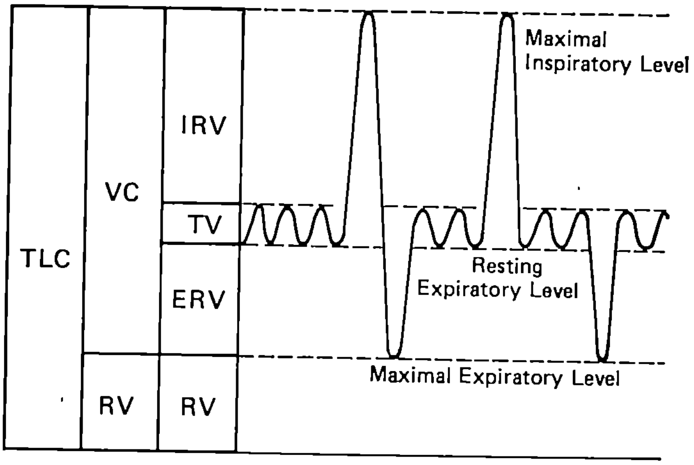


Fig. 1. Spirometric recordings (after Comroe et al. 1962)

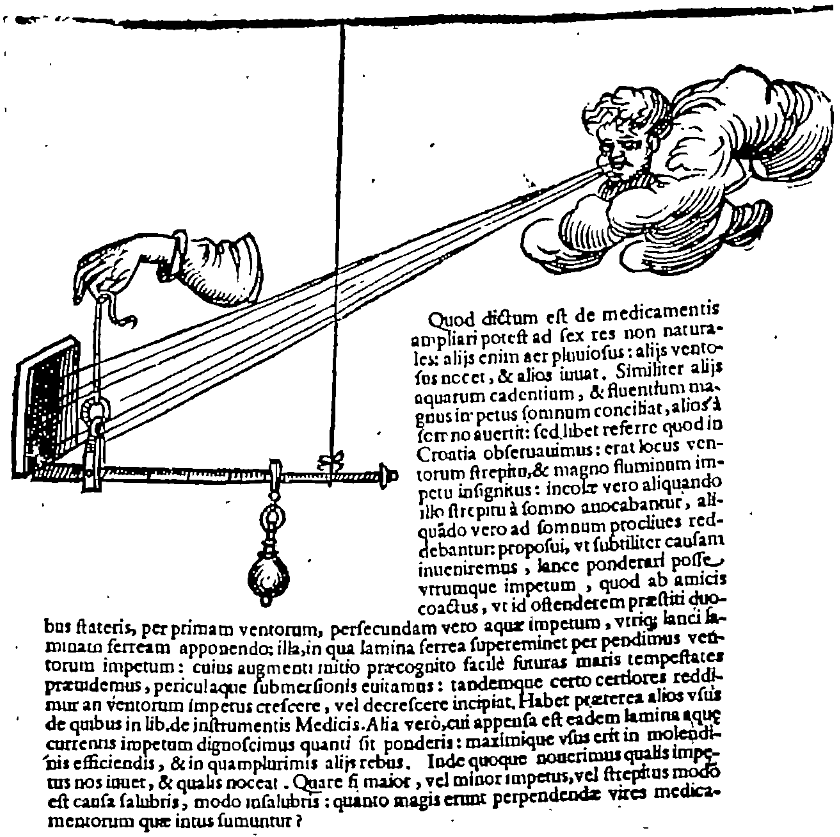
Total lung capacity (TLC) = 6000 ml	Inspiratory reserve volume (IRV) = 3100 ml	Vital capacity (VC) = 4800 ml
	Tidal volume (TV) = 500 ml	
	Expiratory reserve volume (ERV) = 1200 ml	
	Residual volume (RV) = 1200 ml	

EARLY ENDEAVOURS

It would be surprising if the ancients could provide information on these subjects. After all Aristotle (trans. A. L. Peck 1965) thought man had only one lung. But Galen (ed. Kühn 1822), in fact, did do a volumetric experiment on human ventilation. He had a boy breathe in and out of a bladder and found that the volume of gas was, after a period, unchanged. There was, of course, no absolute measurement.

One might expect that it would fall to the iatrophysical school, pioneers of measurement in medicine, to make the first estimations of ventilatory volumes. Even the iatrophysicists were slow. Sanctorius (1660) (Fig. 2) appears to depict a Cupid blowing at a peak flow meter, but the intention turns out to be to illustrate an anemometer for measuring the speed of atmospheric wind; this is all the more tantalizing because Sanctorius was interested in inspiratory volumes in chests of different shapes, and in fever (1632), but appears not to have measured them. And it is surprising that Boyle, Hooke, Lower and Mayow, whose observations on animals founded the study of respiratory physiology, seem to have made no measurements of human ventilatory volumes.

It was the choleric Italian mathematician and physiologist Borelli (1681) who first, so far as we know, tried to measure the volume inspired in one breath. This he did by



Quod dictum eſt de medicamentis ampliari poteſt ad ſex res non naturales: alijs enim aer pluuioſus: alijs ventoſus nocet, & alios iuuat. Similiter alijs aquarum cadentium, & fluentium magnus impetus ſomnum conciliat, alios à ſomno auertit: ſed libet referre quod in Croatia obſeruauimus: erat locus ventorum ſtrepitu, & magno fluminum impetu inſignitus: incolæ vero aliquando illo ſtrepitu à ſomno auocabantur, aliquādo vero ad ſomnum procliues reddebantur: propoſui, vt ſubtiliter cauſam inueniremus, lance ponderari poſſe vtrumque impetum, quod ab amicis coactus, vt id oſtenderem præſtiti duobus ſtateris, per primam ventorum, per ſecundam vero aquæ impetum, vtriq; lanci laminam ferream apponendo: illa, in qua lamina ferrea ſupereminet per pendimus ventorum impetum: cuius augmenti initio præcognito facilè futuras maris tempeſtates præuidemus, periculaque ſubmerſionis euitamus: tandemque certo certiores reddimur an ventorum impetus creſcere, vel decreſcere incipiat. Habet præterea alios vſus de quibus in lib. de inſtrumentis Medicis. Alia verò, cui appenſa eſt eadem lamina aquæ currentis impetum dignoſcimus quanti ſit ponderis: maximique vſus erit in molendinis efficiendis, & in quamplurimis alijs rebus. Inde quoque nouerimus qualis impetus nos iuuet, & qualis noceat. Quare ſi maior, vel minor impetus, vel ſtrepitus modo eſt cauſa ſalubris, modo inſalubris: quanto magis erunt perpendendæ vires medicamentorum quæ intus ſumuntur?

Fig. 2. Sanctorius' anemometer (1660)

sucking a liquid up a cylindrical tube, but his measurement, probably because of the negative pressure required, was far too low, less than 230 ml. Indeed, he himself seems to have observed a discrepancy in comparison with the normal expansion of the chest. James Jurin (1718) was also a mathematician, and had been at Trinity College, Cambridge, in the time of Newton. He then taught at the Newcastle upon Tyne Grammar School, and later became Secretary of the Royal Society, and President of the Royal College of Physicians. He describes with algebraic precision how he blew air into a bladder, having taken care, like Borelli, to occlude the nostrils, and measured the volume of air in the bladder by the principle of Archimedes. His figures for tidal volume of 650 ml and maximal expiration of 3610 ml are not unreasonable. James Keill (1718) of Northampton was a mathematician too, who conducted a controversy with Jurin in the *Philosophical Transactions of the Royal Society* on the force of the heart. He interested himself in respiratory volumes, it seems by direct measurement in corpses. Each lung, he claimed, had a volume of 3700 ml, of which 1230 ml were alveolar.

The Swiss Daniel Bernouilli is referred to in the *Dictionary of Scientific Biography* as 'a typical iatrophysicist under the decisive influence of Borelli and Johann Bernouilli' (his father). He devised (1749) a reasonable method for measuring an expired volume, but unfortunately does not record having used it (Fig. 3). A tube is taken of the form

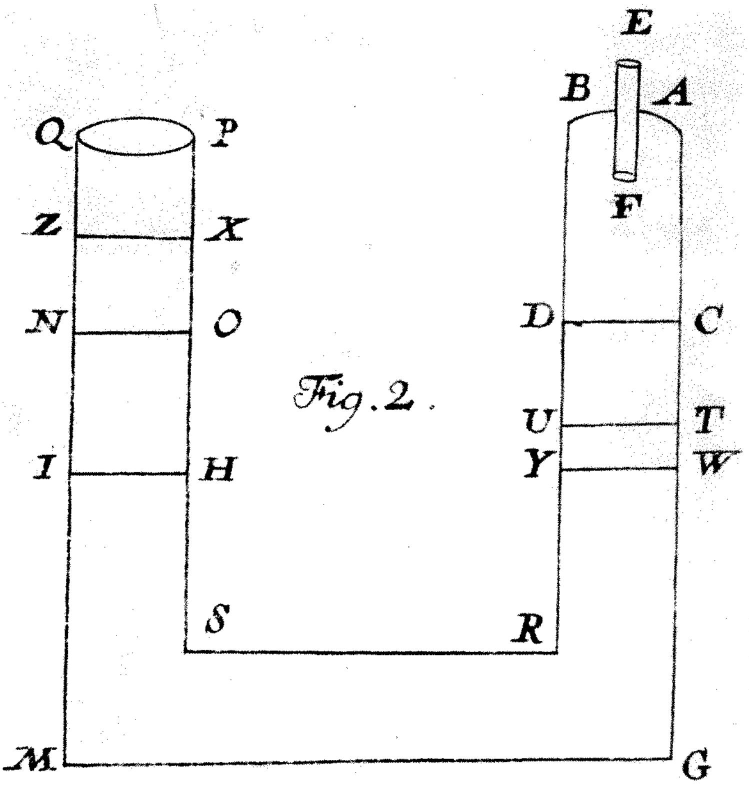


Fig. 3. Daniel Bernouilli's (1749) theory for measuring respiratory volume

shown in his Fig. 2. Water is put in it to the level CDON. Again with the nostrils closed, air is expired into the cavity ABCD, and then a finger closes the orifice E. The water is now at the level UT on the right, and XZ on the left. And in order to correct what we should call the pressure, water is withdrawn from the left-hand limb till the level equals that on the right (WYHI). The volume CDYW is the air expired.

It is not clear how the curate of Teddington, Stephen Hales (1727), measured a maximal expiration, but he quotes Jurin with approval, and obtained a similar figure, 3610 ml. Perhaps he was the first to measure an expiration by the collection of air over

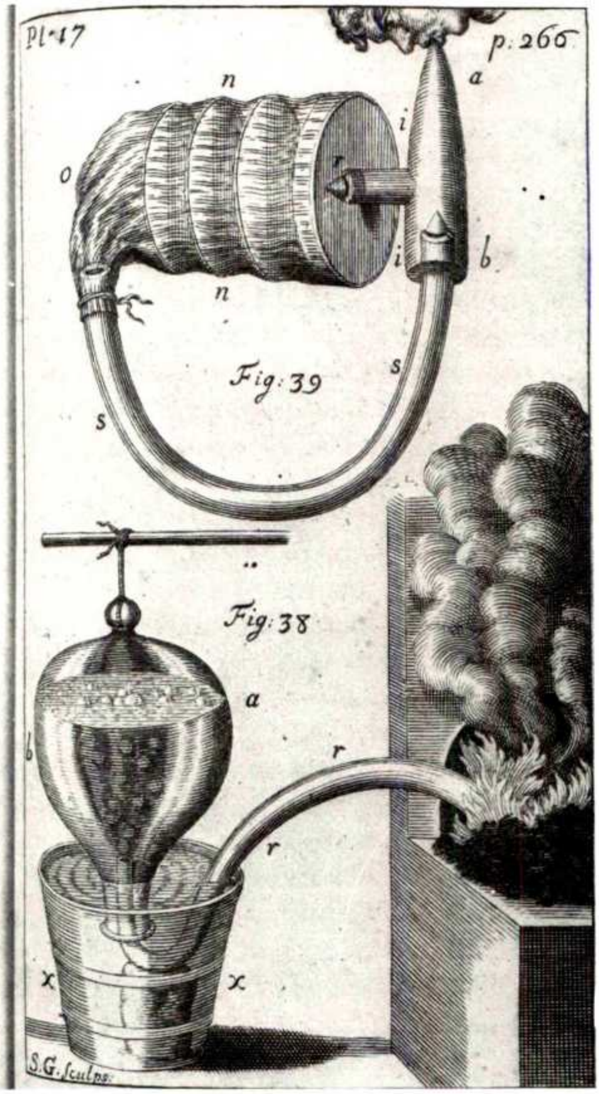


Fig. 4. Stephen Hales' (1727) apparatus for collecting gases over water. The page number at the top has been ingeniously altered from 262, which is correct for the 1727 edition, to 266, correct for the 1769 edition, from which this reproduction has been made. The print is otherwise the same

water, as he described for gases chemically prepared. The Abbé Fontana (1779) gives 570 ml for a maximal expiration, but once more does not describe his technique.

Before we consider gas-holders, mention must be made of Edmund Goodwyn, a London physician (1788) (see Fig. 1 of my Fig. 9), who sucked water a moderate distance into a 'pneumatic vessel' (D) which was weighed on scales. His method carried the same error, though to a lesser degree, as that of Borelli. He did, however, appreciate that the vital capacity could reach as much as 4460 ml. Cotes (1965) points out that Goodwyn was the first to correct for temperature. He did not, however, use a nose-clip.

THE GAS-HOLDER

The credit for this invention goes to the ingenious Stephen Hales (1727), already quoted, though changing volumes of air had been observed over water before then in chemical

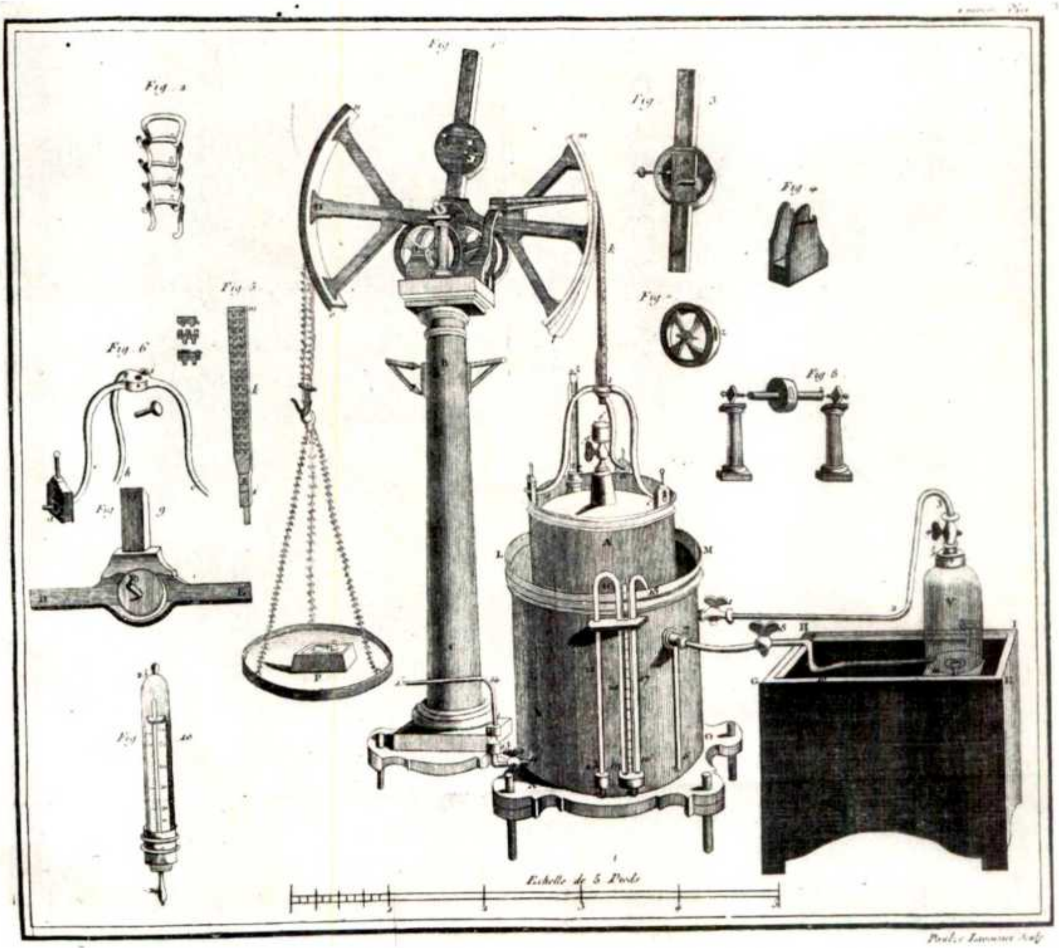


Fig. 5. Lavoisier's gazometer (1789)

and biological experiments (Mayow 1674). Fig. 4 shows Hales' apparatus for collecting a gas, from a furnace in this case, over water. The volume of the gas was not measured nor was that expired by the determined character in 'Fig. 39' of the same plate. Priestley, by 1774, was regularly collecting gases over water.

The large and complicated 'gazometers' of Lavoisier owe much to his scientific collaborator Meusnier, later killed in action against the Prussians in 1793, and his technician Mégnié, who had some of his instruments marked with his name (Daumas 1950). Mégnié spent 91 days on the first one in 1785, excluding his workmen's time, and it cost 636 livres. He then made two better ones, costing between them 7554 livres. I have chosen the illustration (Fig. 5) from Lavoisier's great *Traité Élémentaire de Chimie*, published in 1789, because it records in the bottom right-hand corner that it was engraved by his wife, a pupil of the painter David. Five years later Lavoisier died by the guillotine.

When Abernethy (1793) of St Bartholomew's Hospital wished to ascertain how far expired gases had been depleted of oxygen, he collected them over mercury, and indeed assessed the vital capacity at 3150 ml.

It will come as no surprise that expired volumes were measured at the Pneumatic Institute at Clifton, where James Watt took his consumptive son to see Thomas Beddoes and to breathe the new medicinal gases; they all became high on nitrous oxide with the

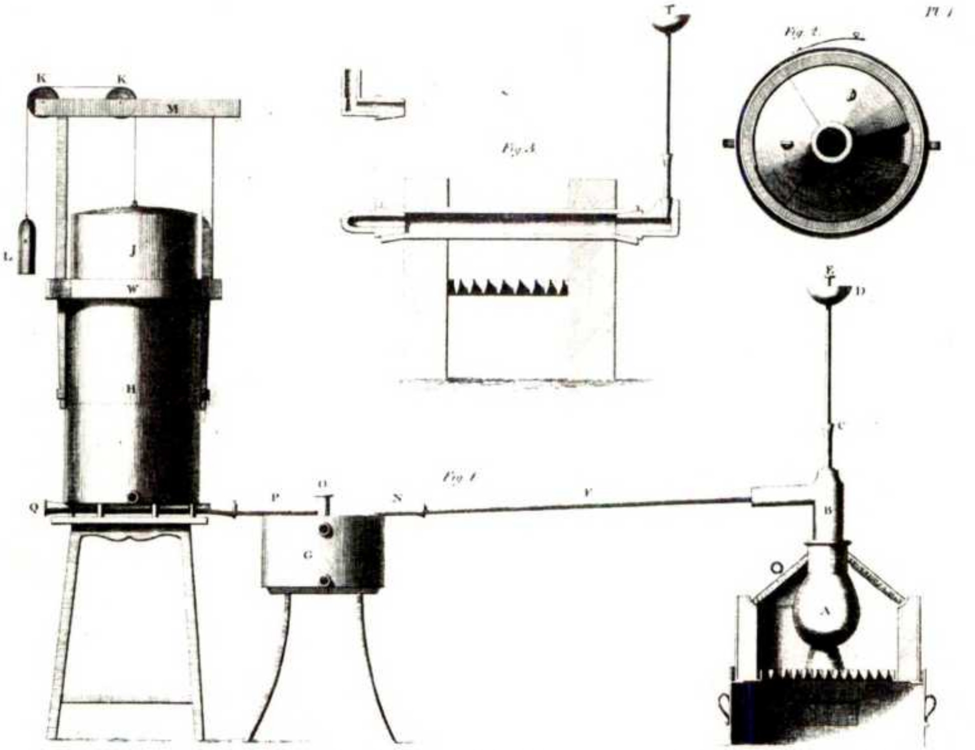


Fig. 6. Watt's 'hydraulic bellows' (HJ) (1794). (*By courtesy of the Wellcome Trustees*)

poets Coleridge and Southey, and Roget of Thesaurus fame (Cartwright 1967). Watt's hydraulic bellows (Beddoes & Watt 1794) (Fig. 6) is a sophisticated instrument, built on the same principles as Lavoisier's apparatus.

A number of the early gasometers used mercury instead of water, to overcome the aqueous solubility of certain gases and the tendency of the water to vaporise. It was the

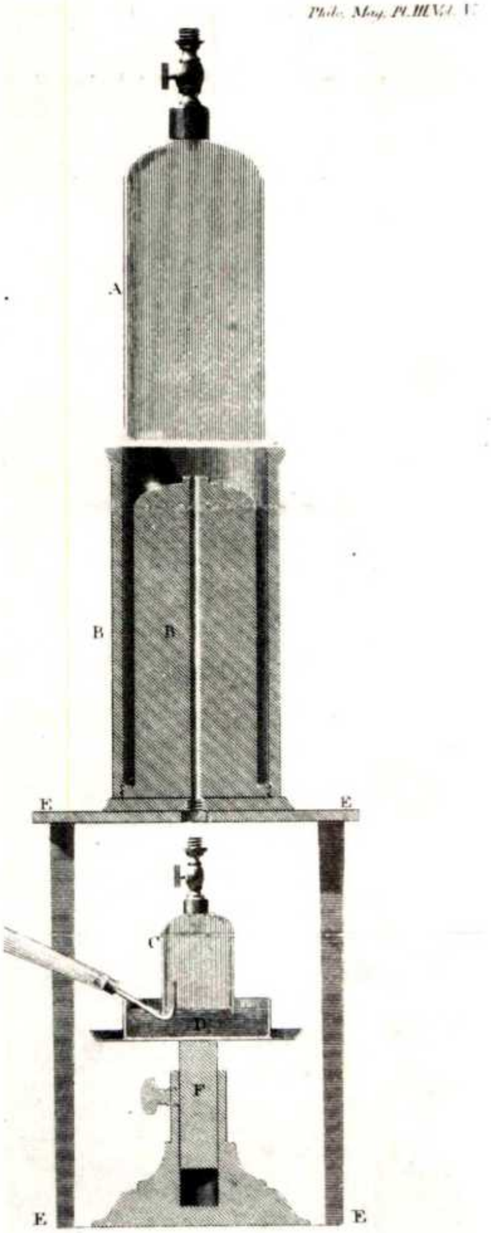


Fig. 7. The 'mercurial gazometer' of W. H. Pepys, jun. (1799)

expense and weight of mercury which induced W. H. Pepys jun. (1799) to construct a gasometer requiring the minimum volume of liquid (Fig. 7). The bell A is of glass, with divisions of capacity marked by a diamond, and the two cylinders, BB, were made of lignum vitae (guaiacum wood), which, unlike tin or copper, resists mercury. Pepys' family were descended from a lord chief justice of Ireland, but his father, W. H. Pepys sen., was a cutler and maker of surgical instruments in the Poultry, London. The son succeeded to his father's business and extended it to making scientific instruments. He also became a distinguished geologist. They were Quakers, and so was his collaborator in the *Philosophical Transactions* paper of 1808, William Allen, who played an international part in the abolition of the slave trade and was a friend of Humphry Davy. This paper illustrates, for physiological experiments, an elaborate apparatus comprising two mercury gasometers and one water gasometer. They found the tidal volume to be 270 ml.

About the same time that Pepys was making his improved gasometer, William Clayfield (1800), from Bristol, having inspected Watt's machine, devised an ingenious refinement. One of the problems with this type of gasometer is the increasing pressure on the gas as the bell rises. Lavoisier's machine, as will be seen from Fig. 5, carried an adjustable counterweight (his 'Fig. 1' and 'Fig. 3') which increased as the bell rose, automatically maintaining atmospheric pressure. Watt's machine had no such device. Clayfield's had a spiral track for the counterweight (H of his 'Fig. 3', in my Fig. 8), which allowed increasing leverage as the bell became heavier, and thus would balance at any point, like Lavoisier's. It was this machine that Humphry Davy used (1800). It may

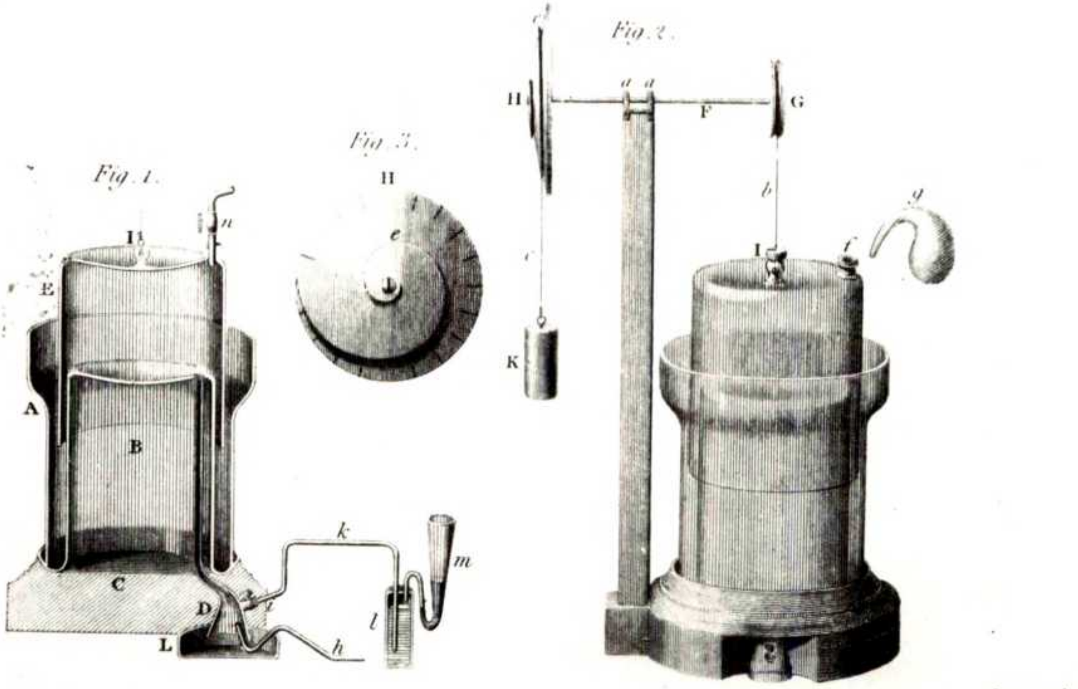


Fig. 8. Clayfield's 'mercurial air-holder', used by Humphry Davy (1800)

be mentioned that one of the copies of the relevant work in the Wellcome Institute is inscribed 'To Dr. Snow from his attached friend Francis Sibson'. Snow was a pioneer in public health and anaesthesia and Sibson is mentioned later in this paper. Davy found his own vital capacity 3110 ml, measured at about 60°F, and his tidal volume 210 ml. He commented that his chest was narrow, and his neck rather long and slender. Davy made another, more remarkable, contribution to pulmonary physiology when he measured the residual volume at between 590 and 600 ml by a hydrogen dilution method. A similar technique was later developed by Gréhant (1864), who does not mention Davy.

OTHER TECHNIQUES

Charles Kite (1795), a Gravesend surgeon, found that the tidal volume was about 280 ml. As I interpret his account he considered the inspiratory reserve volume 3210 ml and the expiratory reserve volume 1430 ml, and he concluded that a moderate sized person could take into and expel from his lungs 4920 ml of air. The technique is not mentioned, but in another experiment he used a bladder.

Body plethysmography, excluding the head, first appears in Robert Menzies' *A Dissertation on Respiration*. Menzies (1796), an Edinburgh medical graduate, attributes to Boerhaave the conception of plunging a man into water in a hogshead up to his chin (see 'Fig. 4,' in my Fig. 9), and measuring the rise and fall of the level in the cylinder round the chin. The volume of fluid displaced by breathing is calculated from the area of the cylinder, less the area of the neck. The Parisian, Richerand (1803), later quotes Boerhaave as actually doing this, but Menzies writes that he knows of no person who has tried this method, and he proceeds to try it himself on two complaisant subjects. The tidal volume proved to be 770 ml in one and 670 ml in the other, he he confirmed these figures with an allantoid (his 'Fig. 2' in my Fig. 9). 'But when [a subject] made a deep inspiration, so much air rushed into the lungs, that the water passed out through the cylindrical vessel'.

Richerand, who has just been quoted, did make some measurements of the quantity of air which could be inspired from a bladder and the quantity which could be expelled into the bell of a pneumato-chemical apparatus. He gives the figure of 490–660 ml for tidal volume, mentioning that Professor Gregory of Edinburgh states in his public lecture that scarcely 160 ml of air enters the lungs at each inspiration.

EARLY NINETEENTH CENTURY—JOHN HUTCHINSON

John Dalton (1813) writes about ventilatory volumes without describing his technique. He estimates his own tidal volume, in modern terms, at nearly 490 ml, the inspiratory reserve volume at 1470 ml, and the vital capacity about 3280 ml. He comments that the quantity of air still remaining in the lungs after forced expiration is not easily determined, having presumably not come across Davy's ingenious work on the subject.

The 'pulmometer' of Edward Kentish (1813) (Fig. 10), physician at Bristol and Clifton, is not usually mentioned in reviews of spirometry. It is the sort of machine that a physician might make up from easily procurable components in what time he was able to make available: in fact, an inverted bell jar standing in water, with entry at its top controlled by a tap, and graduated in pints down the side. It is not clear whether he

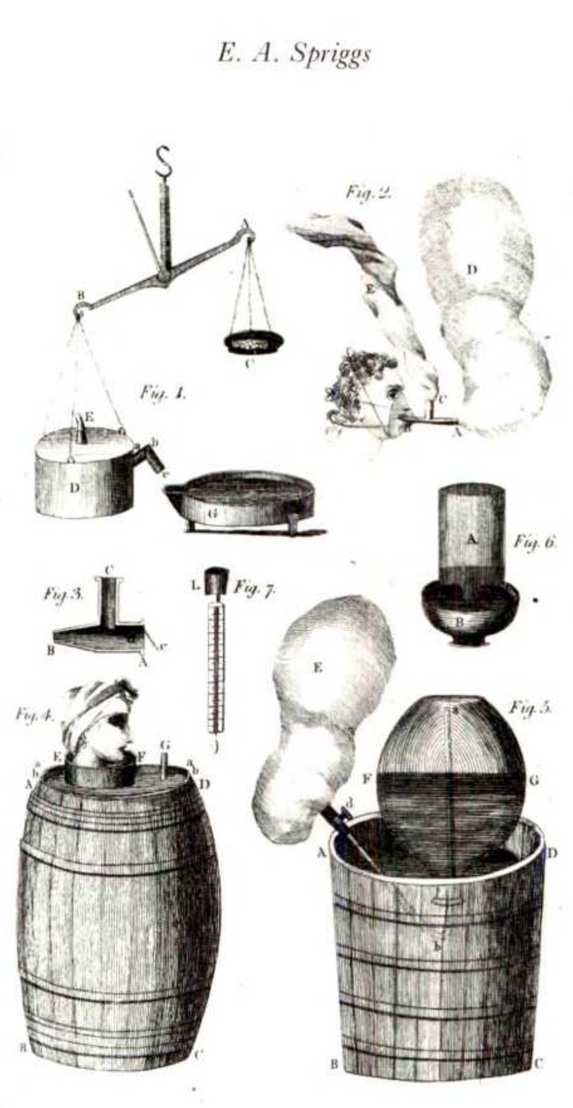


Fig. 1.
Fig. 2.
Fig. 3.
Fig. 4.
Fig. 5.
Fig. 6.
Fig. 7.
A
B
C
D
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G
L

Fig. 9. This page of illustrations is from Menzies (1796). 'Fig. 1' is almost identical with the illustration at the back of Goodwyn's book (1788), and acknowledged as from 'Goodwin' (*sic*). 'Fig. 2' is Menzies' allantoid. 'Fig. 4' illustrates Booerhaave's hogshead to measure body volume

adjusted the pressure after breathing into the jar. His new contribution was to study ventilatory volumes in disease, and we have only asides to show his awareness of normal control studies. 'Mr. S———, aged 17. Phthysis . . . by the Pulmometer he could only inhale [1140 ml] of air. From his stature, he ought, if his lungs had been sound, to have inhaled [4000 ml], if not more'. His three cases of 'bronchitis chronica' are difficult to diagnose from the descriptions and certainly had different natures, but Kentish did appreciate that ventilatory volumes were affected by 'mechanical obstruction' and an 'inflamed state of the bronchiae (*sic*), causing spasmodic action', as well as by pulmonary destruction and pleural fluid.

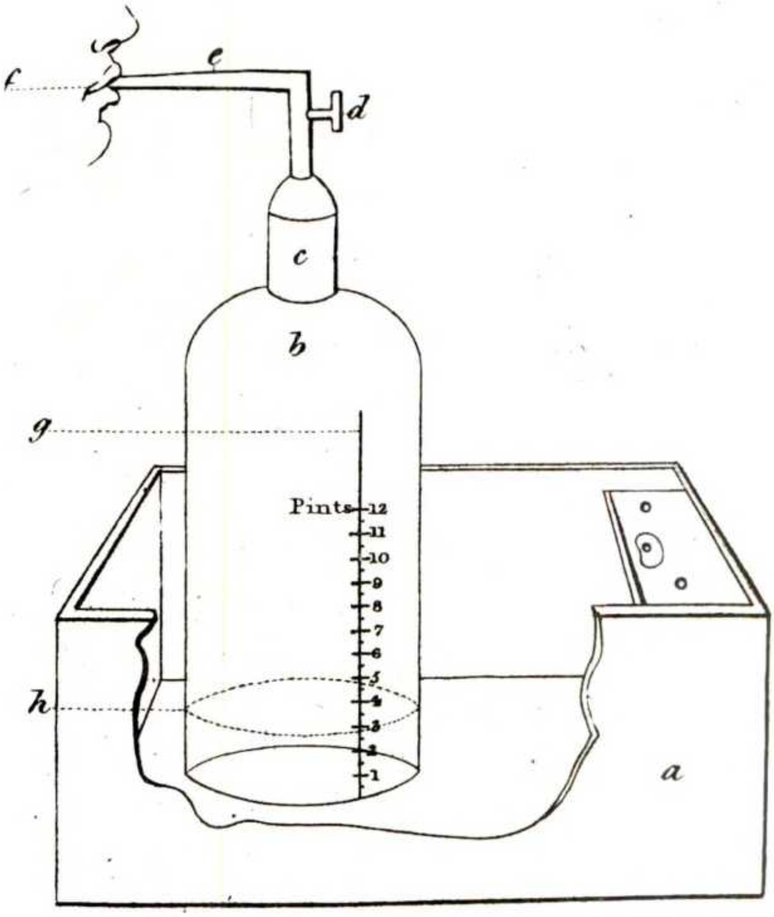


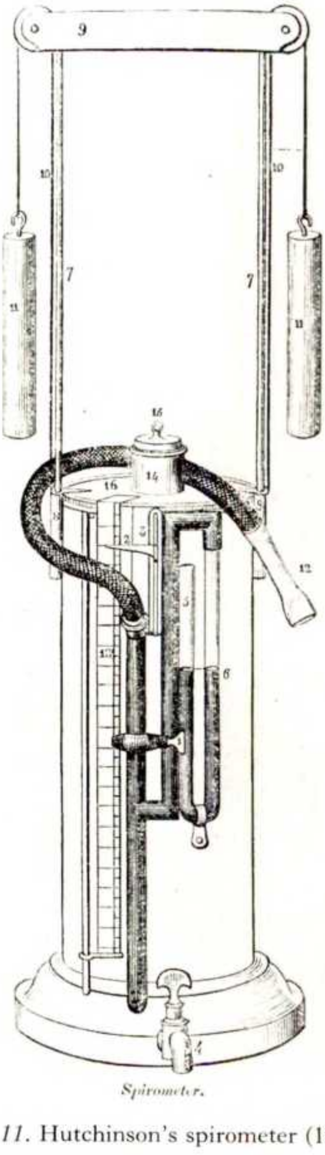
Fig. 10. The 'pulmometer' of Edward Kentish (1813)

In C. T. Thrackrah's classic book *The Effects of the Principal Arts, Trades and Professions . . . on Health and Longevity* . . . (1831) there is also a description of a 'pulmometer'. It is similar to that of Kentish, but air enters the glass jar from beneath. Again, there is no description of correction for pressure, and Thrackrah himself is clear that his machine measures not only respiratory volumes but the power of the expiratory muscles. He suggests the use of such an apparatus in examining recruits for the army. 'Nineteen individuals from the 14th Light Dragoons gave an average of [4280 ml] a man.' Tailors, in spite of the tendencies he notes to curvature of the spine, phthisis, and anal fistula which we now know goes with it ('They are so subject to anal fistula that they have a "Fistula Club"') do not, according to his observations, have reduced ventilation: the average of six individuals was 4360 ml.

It is odd that virtually the same machine, also called a pulmometer, was described by Maddock (1844), who does not mention Kentish or Thrackrah, but attributes the principle of the machine to the late Mr Abernethy. Maddock's letter was stimulated by Hutchinson's description of his spirometer at the Society of Arts.

The water spirometer used today has altered little, except in the addition of graphic and timing devices, and reduction of the mass of the bell, from that of John Hutchinson, a remarkable and versatile character whose career in Newcastle upon Tyne, London, Australia and Fiji is dealt with elsewhere (Spriggs 1977; Gandevia 1977; Bishop 1977), with assessment of his scientific achievements and a bibliography. He should not be confused with the surgeon Jonathan Hutchinson, who was writing at the same time. John Hutchinson (1852) recorded the vital capacities of over 4000 persons and classified them, for example, as paupers, First Battalion Grenadier Guards, pugilists and wrestlers,

Fig. 704.



Spirometer.

Fig. 11. Hutchinson's spirometer (1852)

giants and dwarfs, girls, gentlemen, and diseased cases. He established the linear relationship of the vital capacity to height and showed that it did not relate with weight at any given height. He showed how disease, particularly phthisis, could cause reduction in the measurement, as in the case of Freeman, the American giant and prizefighter, whom he observed over several years. The subject breathing into Hutchinson's spirometer had to be taught to turn a stopcock at the precise moment when he began to expire, and to turn it off at the precise moment when his expiration ceased. Dr Francis Prime tells me there was an original Hutchinson spirometer at the Brompton Hospital till about 1951, but that it cannot now be found.

AFTER HUTCHINSON

Up to this point, an attempt has been made to list most of the publications dealing with spirometry, but from here on it would be tedious to do so. Hutchinson's contributions, which had begun in 1844, were followed by a number of papers on the same subject. Sibson (1848) quoted him, but was more concerned with a 'Chest-Measurer', a very sophisticated caliper, of his own. Herbert Davies (1850), in his course of lectures on 'Physical diagnosis of diseases of the chest', commended Hutchinson's spirometer but preferred a modification introduced by Dr Pereira, with a glass cylinder. Radclyffe Hall (1851) was stimulated to make spirometric measurements on 121 patients in an agricultural part of Cheshire. Fabius (1853) of Amsterdam published in Latin a doctoral thesis *De spirometro ejusque usu*. And in Virchow's *Handbuch der Speciellen Pathologie* (1854) Wintrich writes about 'das englische Spirometer'.

A number of papers described different machines to measure ventilation. Some approximated to Hutchinson's or were simplified or perhaps improved versions. Others took the form of bellows, or a vertical concertina, or were based on the principle of the dry gas-meter, with a dial—one of Hutchinson's machines had this form—or on more complicated conceptions, while some attempted to measure inspiratory or expiratory flow rates (Boudin 1850; Coxeter 1854; Hecht 1855; Guillet 1856; Smith 1857; Mitchell 1859; Bain 1870; Jagielski 1874–5; Holden 1877; Stanley 1891; Denison 1892; Bowen 1906; Maison Mathieu, undated). In the discussion at the Medical Society of London after Jagielski's paper, however, Dr Theodore Williams spoke sadly of the aftermath of Hutchinson's labours: 'At Brompton Hospital his spirometer was not much used, because the patients require education in doing so (*sic*)'. Dr Leared thought 'The instrument was useful in obscure cases, and regretted that its use was discontinued at Brompton Hospital'.

Spirometers with graphic records seems first to have been used by Gad (1879), and by Regnard (1879), and more elaborate closed-circuit machines for volumetric and chemical purposes were elaborated by Tissot (1904), Bohr (1907) and Krogh (1916).

In the first quarter of the present century spirometry appears to have been mainly used by physiologists for teaching and research, by service medical officers in the assessment of recruits, and to a certain extent by physical training enthusiasts. Georges Dreyer, Professor of Pathology at Oxford, seems to have resuscitated its use (1919) and Myers wrote a monograph on the vital capacity in 1925. So often physicians are content with relatively inaccurate diagnostic tools till surgical progress compels them to refine their techniques. If they do not, they are then shown up at operation or by its consequences. And so it was that the development of thoracic surgery stimulated a Medical Research Council Special Report (Moncrieff 1934) on tests for respiratory efficiency.

The amount of air which a subject can inspire (and expire) in a minute, the maximum voluntary ventilation, was first measured by Hermannsen in 1933. The usual cause of limitation of the figure is airways obstruction, and it is said that physicians have in the past judged this by patients' ability to blow out a candle. More recently W. A. Briscoe (Olsen 1962) has originated a simple test in which the subject attempts to blow out a lighted match under standard conditions. A more accurate method of measuring airways obstruction is to time the movement of air in a single breath. According to Gaensler (1951) this was first done by R. A. Bruce, but Tiffeneau and Pinelli (1948) may have priority. Gaensler interpreted his results on the principle that an asthmatic, say, is able to push out only a small proportion of his vital capacity in the first second. The most accurate measurements of airways resistance are made with a whole body plethysmograph (DuBois & van de Woestijne 1969), but now the peak flow meter (Wright & McKerrow 1959) or one of the cheaper and lighter developments of it (Campbell et al. 1974) gives us rapid information in the ward, clinic or surgery; or, indeed, the patient can make repeated observations in the home.

CONCLUSION

It is interesting to examine the reasons why these men perfected their apparatus and made their measurements. Curiosity, in a wide sense, is often a principal reason for scientific advance. Then measurement has been an obsession in medicine since the time of the iatrophysicists. It was not until the early nineteenth century that any application was attempted of respiratory measurement to disease, but since that time the clinical approach has been dominant and thoracic surgery has proved a special stimulus to spirometry.

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Since writing this paper the author's attention has been drawn to three early publications about timed expiratory measurements:

Barach, Alvan L. (1938) Physiological methods in the treatment of asthma and emphysema. *Ann. intern. Med. 12*, 454.

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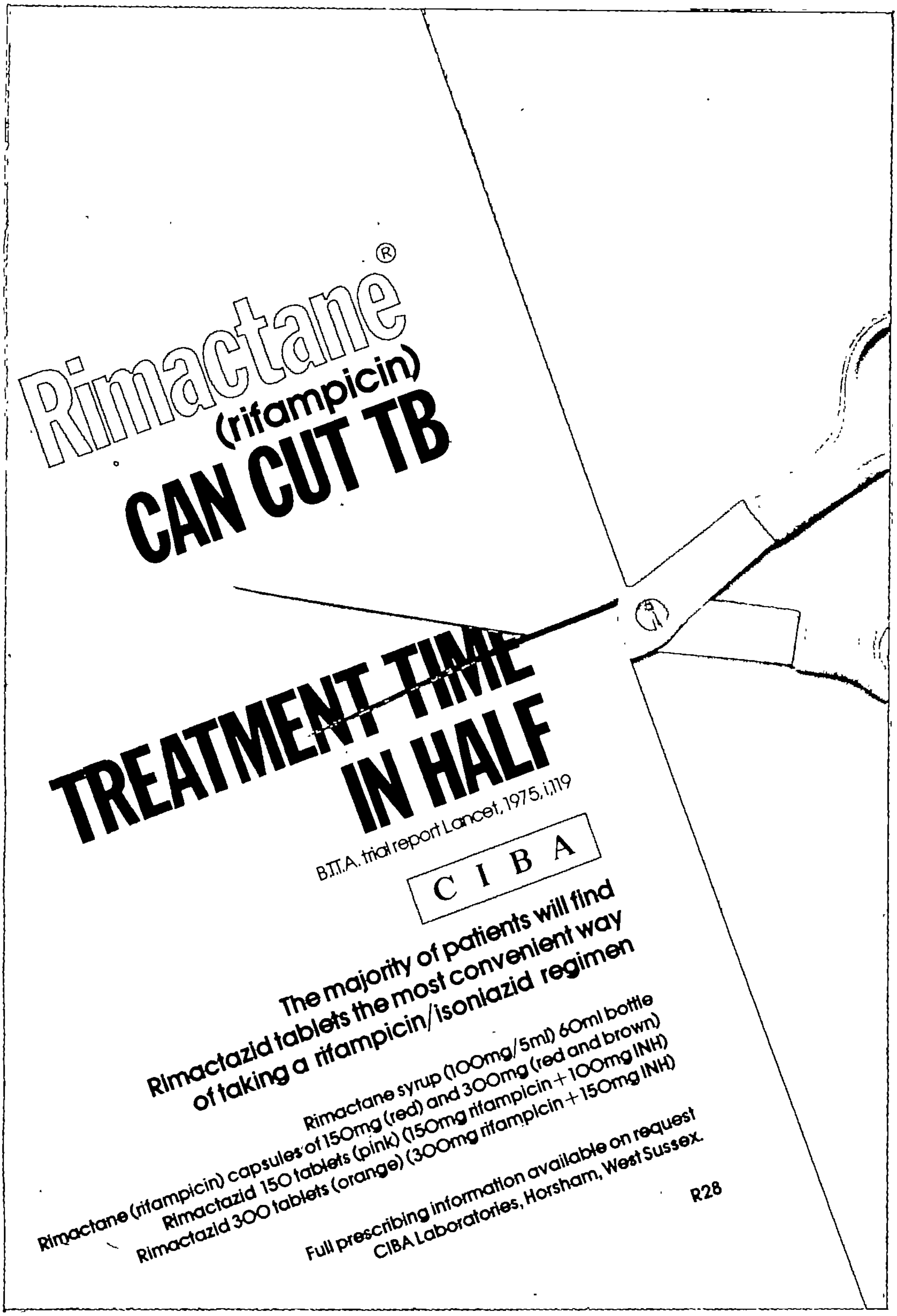

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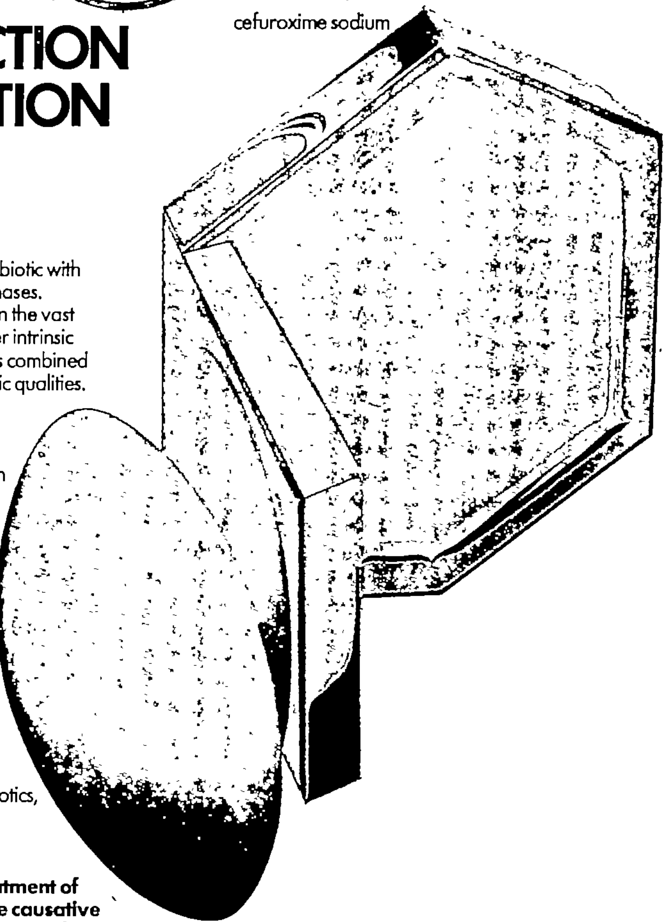

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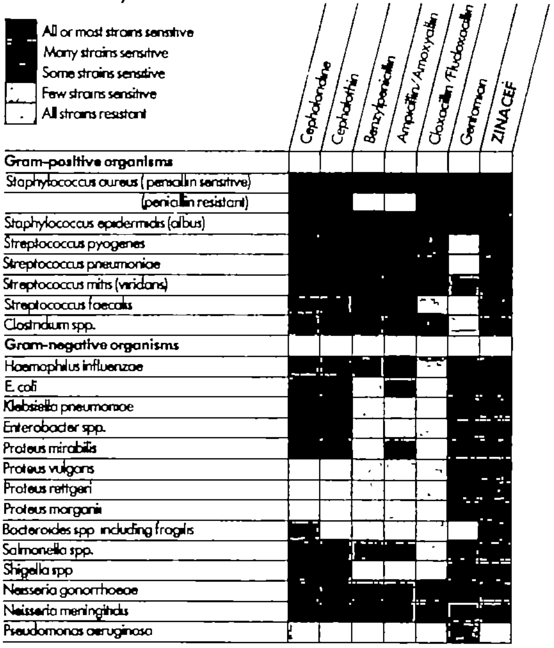

■ All or most strains sensitive
■ Many strains sensitive
■ Some strains sensitive
□ Few strains sensitive
□ All strains resistant

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Gram-positive organisms							
Staphylococcus aureus (penicillin sensitive)	■	■	■	■	■	■	■
(penicillin resistant)	■	■	□	□	■	■	■
Staphylococcus epidermidis (albus)	■	■	■	■	■	■	■
Streptococcus pyogenes	■	■	■	■	■	□	■
Streptococcus pneumoniae	■	■	■	■	■	□	■
Streptococcus mitis (viridans)	■	■	■	■	■	■	■
Streptococcus faecalis	■	■	■	■	□	□	■
Clostridium spp.	■	■	■	■	■	□	■
Gram-negative organisms							
Haemophilus influenzae	■	■	■	■	□	■	■
E. coli	■	■	□	■	□	■	■
Klebsiella pneumoniae	■	■	□	□	□	■	■
Enterobacter spp.	■	■	□	□	□	■	■
Proteus mirabilis	■	■	□	■	□	■	■
Proteus vulgaris	□	□	□	□	□	■	■
Proteus rettgeri	□	□	□	□	□	■	■
Proteus morganii	□	□	□	□	□	■	■
Bacteroides spp including fragilis	■	□	□	□	□	□	■
Salmonella spp.	■	■	■	■	□	■	■
Shigella spp	■	■	□	□	□	■	■
Neisseria gonorrhoeae	■	■	■	■	■	■	■
Neisseria meningitidis	■	■	■	■	■	■	■
Pseudomonas aeruginosa	□	□	□	□	□	■	□

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Obstetric and gynaecological infections	Meningitis
	Gonorrhoea

Dosage
Adults: Generally 750mg t.d.s. I.M. or I.V. Severe infections 1·5 gram t.d.s. I.V. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in 3 or 4 divided doses. 60 mg/kg/day will be appropriate for most infections.
Neonates: 30 to 100mg/kg/day in 2 or 3 divided doses
Gonorrhoea: Single dose of 1·5 gram (2x750mg I.M. into different sites)

Contra-indications
Hypersensitivity to cephalosporins

Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, cefuroxime should be administered with caution during the early months of pregnancy.
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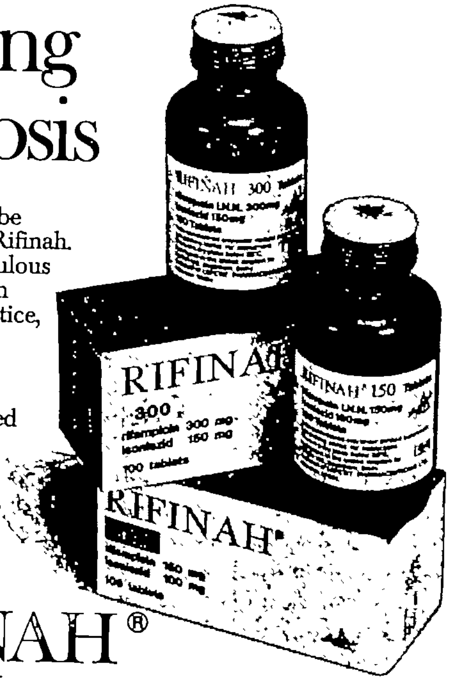

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Br. J. Dis. Chest (1978) *72*, 181

IPRATROPIUM BROMIDE, SALBUTAMOL AND PREDNISOLONE IN BRONCHIAL ASTHMA AND CHRONIC BRONCHITIS

I. M. Lightbody, C. G. Ingram, J. S. Legge and R. N. Johnston

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Department of Clinical Measurement, Ninewells Hospital, Dundee

Summary

Eleven patients with bronchial asthma and 10 with chronic bronchitis were treated over four consecutive 3-day periods, firstly with aerosols either of ipratropium bromide (40 μg four times a day) or of salbutamol (200 μg four times daily) by random allocation, then the alternate drug, next by both drugs together, and finally with prednisolone (10 mg three times daily) in addition to both drugs. The effects of these four treatment periods were assessed both clinically and by measuring ventilatory capacity, nitrogen slope and progressive exercise testing.

Ipratropium bromide and salbutamol produced approximately equal improvements in both diseases, with salbutamol showing a marginal advantage in patients with asthma. The combination of both drugs together more than doubled the FEV_1 change in both groups of patients. The addition of prednisolone to both drugs produced a marginal advantage only in those with asthma.

INTRODUCTION

Many patients with bronchial asthma as well as those with chronic bronchitis with airway narrowing fail to reach their predicted ventilatory function after a bronchodilator. The purpose of this paper is to examine the effects of a new anticholinergic drug (ipratropium bromide), to compare it with a known β_2-adrenergic stimulator (salbutamol), to study these drugs in combination, and finally to see what further improvement could be obtained with corticosteroid treatment in addition to both drugs. Since earlier studies (Poppius & Salorinne 1973; Gross 1975; Petrie & Palmer 1975) have examined mainly the immediate effects of ipratropium bromide we chose to study the effects of these drugs over 3-day periods on in-patients. We considered longer periods of individual treatment but this became impracticable if each patient were to act as his own control. An additional aim of the study was to look for evidence in support of the claim that ipratropium bromide is more effective in patients with bronchitis (Poppius & Salorinne 1973).

Petrie and Palmer (1975) have shown in single-dose experiments that a dose of 200 μg of salbutamol equates with 40 μg of ipratropium bromide, the peak response of forced expiratory volume in one second (FEV_1) occurring 1 hour after salbutamol and 2 hours after ipratropium bromide, with very little decline during a further 2 hours. Thus ipratropium bromide had a more prolonged action, but the response in asthmatic patients was less than that produced by salbutamol. Gross (1975) found the onset of action of ipratropium bromide was 15–30 min and its effect persisted for 4 hours, and dose-response experiments showed maximal bronchodilation, as measured by FEV_1 and maximal mid expiratory flow (MMEF), to be achieved by 10–20 μg. In 10 patients with asthma, they found the increase in MMEF to be significantly greater than that of FEV_1, suggesting a greater effect on peripheral than on large airways. Storms et al. (1975), however, examining the effect of ipratropium bromide in 10 patients with asthma, concluded that the major effect of the drug in relieving bronchoconstriction appeared to be in the large airways.

Patients and Methods

Twenty-one in-patients were studied, 11 with bronchial asthma and 10 suffering from chronic bronchitis with reversible airway narrowing. The diagnosis of chronic bronchitis followed the Medical Research Council criteria for chronic obstructive bronchitis (1965) and that of asthma on previously agreed criteria (Ciba Guest Symposium 1959). Patients with the following conditions were excluded: pregnancy, hypersensitivity to atropine, glaucoma, hepatic, renal or overt cardiovascular disease or thyrotoxicosis. All therapy was stopped before the study in 14 patients, but in the remaining 7 base-line therapy with either prednisolone or beclomethasone by aerosol was continued in addition to the drugs under trial. Informed consent was obtained in each case. No patient smoked while the study was in progress.

Treatment comprised four consecutive 3-day periods after a pre-trial 2-day assessment. Patients were aware of the difference in aerosols, many having previously received salbutamol or beclomethasone, but the doctors performing the clinical assessments and pulmonary function tests were unaware of individual treatments. Allocation to the order of salbutamol or ipratropium bromide in the first two treatment periods was by random selection with each drug given singly. Thereafter salbutamol and ipratropium bromide were given together and whichever drug was administered in the first 3-day period was the first to be given when both drugs were used in combination. The last 3-day treatment was with salbutamol, ipratropium bromide and prednisolone. The dose of salbutamol was 200 μg (two puffs) at 08.00, 12.00, 18.00 and 22.00 hours, ipratropium bromide 40 μg (two puffs) at similar times, and prednisolone 10 mg three times daily.

Each day patients were asked if they noticed any change in their condition compared with the pre-treatment state and this was recorded as: 1 worse than usual; 2 same as usual; 3 better than usual; 4 very much better than usual. A similar scale was used to score the physician's assessment of bronchoconstriction and any side effects were recorded. Pourability of sputum by inversion of the container was assessed on the following scale: 1 adheres to base; 2 slow movement; and 3 free movement. Pulse rate and blood pressure were recorded twice daily. Blood eosinophilia was measured and expressed as a percentage of the total white cell count. The volume expired in the first second of a forced expiration (FEV_1) and the total volume expired were measured with a dry bellows spirometer (Vitalograph). The best of three measurements was recorded and the test repeated 15 min after two puffs (200 μg salbutamol) and the percentage improvement calculated. Subsequently, FEV_1 measurements were repeated at 9.00 and 17.00 hours daily. This study was not designed to examine diurnal variation since the morning measurements were made after the administration of the bronchodilator drugs. Two other measurements were made from the forced expirogram, the maximum mid-expiratory flow ($FEF_{25-75\%}$) and the mean forced expiratory flow from 75 to 85% of the forced expiration ($FEF_{75-85\%}$) (Morris et al. 1975). All volumes were expressed at BTPS. Additional measurements were made at the end of each treatment period whenever possible. A flow volume curve of forced expiration was recorded with a dry electric spirometer (Electro/med 780) and an XY plotter (Bryans 22020) from which were obtained the flow rates at 50% and 75% of vital capacity ($FEF_{50\%}$ and $FEF_{75\%}$). A single breath oxygen test of ventilatory distribution was performed following an agreed protocol (National Heart and

Lung Institute 1973) using a mass spectrometer (Centronic Q806) and an electric spirometer, the signals being recorded on the XY plotter. The slope of phase III was determined by drawing the best-fit line between 70% vital capacity and the onset of phase IV. This slope was expressed as change in nitrogen percentage per litre of expired gas.

Progressive exercise tests were carried out on an electrically braked bicycle ergometer (Godart). The rate of work for the first minute was 25 Watts and this was increased at 1 min intervals by 25 Watts until the patient was unable to continue. An electrocardiogram was continuously monitored. A simple assessment of exercise tolerance was made by expressing the work performed in Joules, which gives a measure of the rate of work achieved and of the length of time exercise was performed (1 Watt = 1 Joule/second). Two-way analyses of variance were done on all the measurements.

RESULTS

The clinical assessment measurements were conflicting and underlined the well known limitations of these observations. The pre-trial measurements are shown in Table I and the results of treatment in Table II. The FEV_1 results were the best readings obtained on the third day of each treatment period. The means of all readings showed no difference. Clinical and FEV_1 measurements were complete in all patients and the $FEF_{25-75\%}$ and $FEF_{75-85\%}$ in all but two patients. Because the respiratory function laboratory was in a separate hospital it was not possible at the end of each 3-day period to complete all

Table I. Pre-trial measurements (mean and range)

	All patients	*Asthma*	*Bronchitis*
Age	47 (16–70)	36.5 (13–60)	52 (38–70)
FEV_1 (ml)	1360 (600–2900)	1400 (600–2900)	1280 (750–2500)
Improvement (%)	21 (6–50)	25 (9–45)	15.6 (6–50)

Table II. Mean numerical improvement by treatment and disease

	Disease	*Patient response*	*Clinical assessment*	*FEV_1* (ml)
No. examined	Asthma	11	11	11
	Bronchitis	10	10	10
Ipratropium bromide	Asthma	0.1	0	190
	Bronchitis	0.6	0.4	190
Salbutamol	Asthma	0.27	0.1	300
	Bronchitis	0.5	0.4	170
Both	Asthma	0.8	0.9	520*
	Bronchitis	0.3	0.4	470
Triple therapy	Asthma	1.1	1.3	790†
	Bronchitis	1.3	1.1	460

*P 0.01 compared with mean improvement with both drugs separately.
†P 0.1 compared with results on both drugs together.

the tests and complete records were obtained in 8 patients (nitrogen slope), 7 patients (flow volume measurements) and 8 patients (progressive exercise testing). The patients already on maintenance steroid treatment showed no significant difference in their responses compared with the main group on no other treatment. The observations which have discriminated best between treatments were the FEV_1 recordings and the patient assessment index. The FEV_1 measurements have shown that both drugs by themselves produce improvements compared with base-line measurements, but when given together the FEV_1 increase was more than doubled. The addition of prednisolone produced further improvement only in those with asthma (Fig. 1).

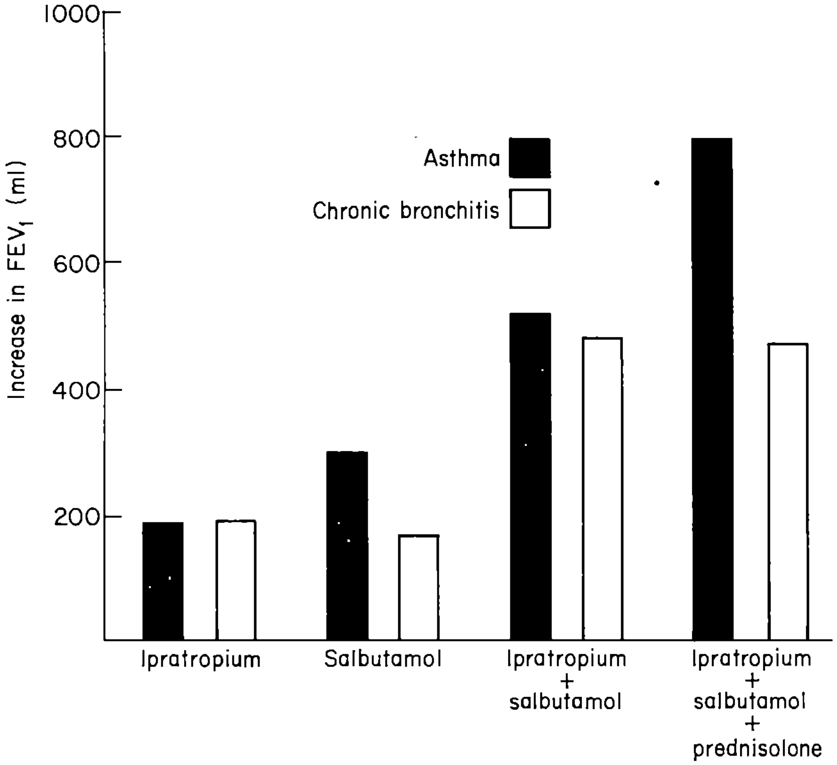

Fig. 1. Results in four groups of patients

Despite selection of patients with clear response to salbutamol and an FEV_1 near 50% of normal we found that 5 patients at the time of this study showed little variation in the serial FEV_1 measurements and these poor responders have made the overall assessments of response to drugs more difficult. These patients comprised four in whom the FEV_1 variation throughout the whole study was only 100 ml and one showing no variation at all. These 5 patients did not respond to either drug nor the drugs in combination. In the converse group, i.e. those showing a maximal response in FEV_1 (11 patients: 8 asthmatic and 3 bronchitic), the improvement in FEV_1 with ipratropium bromide and salbutamol approximated, but the $FEF_{75\%}$ response to ipratropium bromide was greater ($P < 0.07$).

The further tests of airway function have failed to show any significant advantage to either drug or drug combination over that already apparent from the FEV_1 results. Functional residual capacity (FRC) measurements were available both before and on completion of the study in 14 patients. Twelve of these patients showed clinical improvement but there was no significant change in the FRC measurements (mean FRC pre-trial 3.7 litres and post-trial 3.8 litres). None of the bronchitic patients had a blood eosinophilia but 27% of patients with asthma had an eosinophilia of 10% or greater.

There was no difference in the purability of the sputum in those receiving ipratropium bromide compared with those on salbutamol.

No untoward side effects were observed with any of the treatment regimens.

DISCUSSION

The dose of salbutamol used in the study is widely accepted in present clinical practice. Single dose response experiments with salbutamol have shown an increase in air way conductance with doses up to 500 μg (Warrel et al. 1970) but in view of the reported resistance to β-adrenergic agonists in patients receiving more prolonged salbutamol (Holgate & Tattersfield 1976) we consider that our present dose of salbutamol was appropriate. Moreover it is logical to use safe doses of individual drugs in combination rather than increasing individual drugs dosage to possible toxic levels.

The principal result in this study has been evidence for summation of improvement when both ipratropium bromide and salbutamol are combined, and this may well be the future role for this new anticholinergic drug. This additive action is equally effective in asthma and chronic obstructive bronchitis. The anticholinergic action of ipratropium bromide did not affect sputum production or pourability in the bronchitic patients. The response to bronchodilators in chronic airway obstruction is limited by various factors, notably those imposed by structural changes in the bronchi such that only a limited response is possible to any bronchodilator drug. The fact that prednisolone in our patients failed to produce significant improvements in the FEV_1 is additional evidence of long-standing airway obstruction. The clinical and subjective improvements in our patients were not due to reductions in the FRC as reported by Woolcock and Read (1965). In 5 of 8 patients progressive exercise testing did improve with prednisolone but there was no difference between the individual effects of salbutamol and ipratropium bromide. Since prednisolone was always the final treatment some of the increase in exercise capacity may well have been due to a training effect but there is only evidence for this in one patient. Close volume measurements are frequently unobtainable in patients with moderately advanced airway obstruction and this was again found in our patients. Calculation of the nitrogen slope failed to detect significant difference between the two drugs.

Improvement in exercise testing was seen in those receiving both ipratropium bromide and salbutamol together but the difference did not reach statistical significance.

There is experimental evidence pointing to increased vagal activity contributing to bronchospasm (Gold et al. 1972). Vagal activity may well vary at different times, however, and the benefit of an anticholinergic drug be evident only when this activity is maximal. In patients where vagal activity is variable more prolonged treatment with ipratropium bromide may be required.

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We conclude that ipratropium bromide merits more prolonged study in combination with salbutamol in patients with reversible airway obstruction.

ACKNOWLEDGEMENTS

We acknowledge the technical help of Mrs P. Reid, advice on statistical analysis by Mr S. Ogston, and Dr G. A. Cox of Boehringer Ingelheim who provided the ipratropium bromide.

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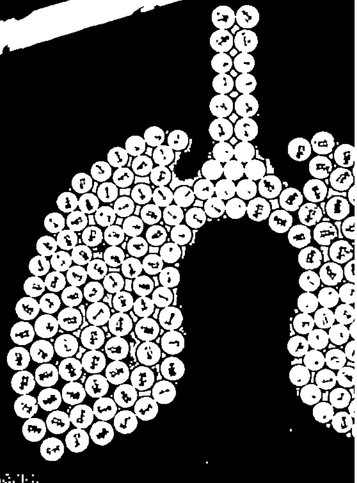

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Br. J. Dis. Chest (1978) *72*, 187

PLEUROPULMONARY LUNG INFECTION BY ANAEROBIC BACTERIA

ROHINI L. ABEYSUNDERE, MARGARET E. HODSON, MELVYN SZAWATKOWSKI AND PAUL NOONE

Royal Free Hospital and Brompton Hospital, London

Summary

Two patients with severe pleuropulmonary infection caused by non-sporing anaerobic bacteria are described. One had an empyema with foul-smelling pus and developed bacteraemia, and the other developed a lung abscess. Both were successfully treated with antibiotics and drainage, chest surgery being avoided. The successful diagnosis and treatment of these patients involved close liaison between clinical and laboratory staff.

INTRODUCTION

Although anaerobic bacteria were first described by Pasteur in 1861, their danger as pathogens was not fully appreciated until the last decade when important technological advances in the routine laboratory isolation and identification of these organisms were made (Holdeman & Moore 1972; Sutter et al. 1972).

The role of non-sporing anaerobic bacteria alone, or associated with facultative anaerobic bacteria as pathogenic agents in lung infections was first reported in 1904 (Guillemot et al. 1904) and more recently by Bartlett et al. (1974). Reports of anaerobic bacteria causing lung infection have been much less frequent in the UK. This is partly because sputum specimens are not routinely cultured for anaerobic bacteria and also because sputum specimens are always contaminated by the mouth flora which includes anaerobic bacteria in large numbers and so does not give a true indication of the infecting agent. In the USA this problem has been partly overcome by the use of transtracheal aspiration for sputum collection (Bartlet et al. 1973). This technique is not popular in Britain.

Two patients with pleuropulmonary infection where non-sporing anaerobic bacteria were the major pathogens are described. Both patients responded to appropriate chemotherapy.

Materials and Methods

Sputum was examined macroscopically for purulence and odour.

It was then homogenized in a stomacher (Mitchell & Hardy 1975) and cultured in dilutions of 1:2 and $1{:}10^{-4}$ in quarter strength Ringer's solution on chocolate agar (Oxoid) in an atmosphere containing 10% carbon dioxide and on Columbia blood agar (Oxoid) aerobically at 37°C. Sputum was also cultured for at least 48 hours anaerobically on *Brucella* agar (BBL) containing 5 μg/ml haemin, 0.5 μg/ml menadione and 70 μg/ml neomycin sulphate in the Gaspak system (hydrogen + carbon dioxide) at 37°C. Gram and auramine stains (for acid-fast bacilli) on direct smears were

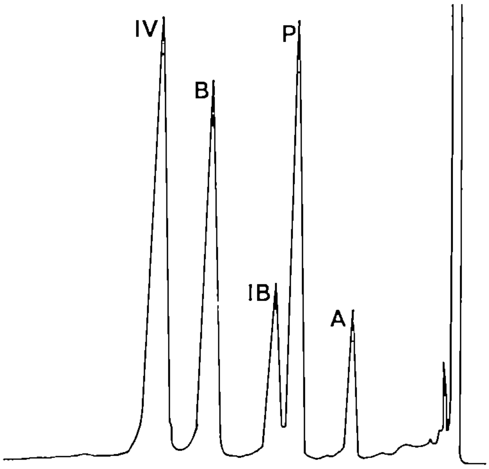

Fig. 1. Gas–liquid chromatogram obtained from the sputum of Case 1. This pattern indicates infection with *B. melaninogenicus*

A = acetic acid		P = propionic acid
IB = i-butyric acid		B = butyric acid
IV = i-valeric acid		

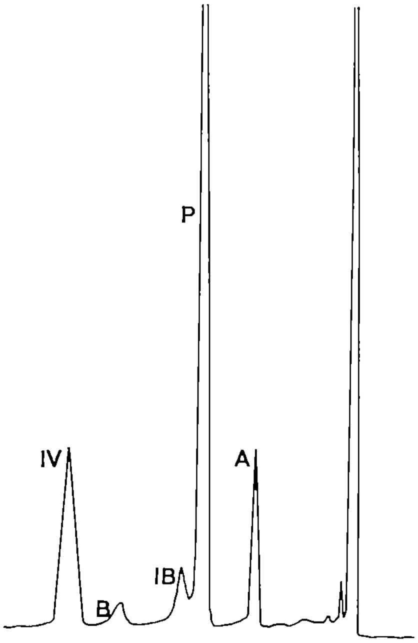

Fig. 2. Gas–liquid chromatogram obtained from the empyema fluid of Case 2. This pattern indicated infection with *B. fragilis*. Key as Fig. 1

made routinely on every sputum sample. Pus samples aspirated from the empyema were cultured in a similar manner.

Blood cultures were taken into three bottles: nutrient broth (Southern Group) with a castenada slope and incubated in 10% carbon dioxide, tryptose soy broth (Difco) and thiol broth (Difco). The contents were subcultured at 24 and 48 hours and then weekly for at least 2 weeks, or immediately if turbidity suggested bacterial growth. Anaerobic subcultures from thiol broth were carried out as for sputum samples.

All aerobic and facultative anaerobic bacteria isolated were identified according to the methods and tables of Cowan and Steel (1974). The anaerobic bacteria were characterized and identified by their growth on BBL *Brucella* agar, Nissui *Fusobacterium* agar, and Nissui *Bacteroides* agar (Ohtani 1970), by the use of API sugars (Starr et al. 1973), by differential antibiotic sensitivity tests (Holdeman & Moore 1972; Sutter et al. 1972) and by GLC pattern (Holdeman & Moore 1972).

Antibiotic sensitivity tests were performed according to Stokes' disc diffusion method (Stokes 1968) using Oxford *Staphylococcus aureus* (NCTC strain 6571) or *Bacteroides fragilis* (WAL strain 1) as control organisms. Gentamicin assay was performed using the urease method which has been validated in routine use in this laboratory (Noone et al. 1974).

Gas–liquid chromatography (GLC) was carried out using a Pye Unicam 104 which was programmed to detect the presence of volatile fatty acids. These are the end products of metabolism of glucose by anaerobic bacteria each organism producing a characteristic pattern of fatty acids (Gorbach et al. 1974). The volatile fatty acids were detected by chromatographic examination of either pure liquid subcultures of anaerobic bacterial isolates, or sputum and pus specimens inoculated directly or after ether extraction (Figs 1, 2). This technique enables speciation of anaerobic bacteria and has the advantage of being rapid, the result being available 1½ hours after the specimen is received by the laboratory.

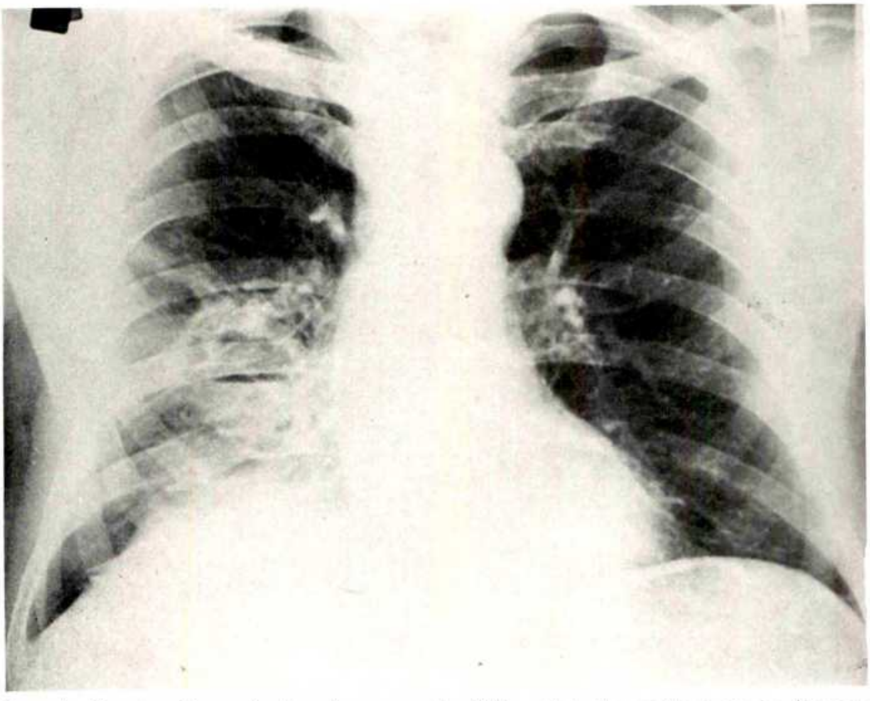

Fig. 3. Case 1. Chest radiograph showing a poorly differentiated opacity 5 cm in diameter and a fluid level in the anterior segment of the right upper lobe extending across the fissure into the middle lobe. There is patchy shadowing in the right lower lobe

Case Reports

Case 1

Case 1 was a 57-year-old man with carious teeth and gingivitis. He was admitted complaining of pyrexia, cough, dyspnoea and right-sided pleuritic pain of one week's duration. There was collapse and consolidation in the right lower lobe. Blood cultures taken before therapy failed to grow organisms. Sputum was cultured and revealed a scanty growth of *Haemophilus influenzae*, although at least 5 subsequent sputum cultures grew commensal flora only. The patient was treated with physiotherapy, ampicillin 500 mg four times daily and flucloxacillin 500 mg four times daily, both intramuscularly for one week and then orally for another week. His chest radiograph appearance improved and he was discharged home.

The patient was re-admitted two weeks later complaining that he felt ill and he was coughing up 'four teacupfuls' of foul-smelling sputum each day. He had been vomiting at home. The chest radiograph at this time showed a lung abscess. Bronchoscopy performed at this stage revealed no foreign body or malignancy. Auramine stains for acid-fast bacilli were consistently negative. Cytological studies of sputum were also negative for malignant cells.

The patient was very ill and deteriorating clinically. Infection with anaerobic bacteria was strongly suspected, and treatment with metronidazole 800 mg three times daily and ampicillin 500 mg four times daily, both orally, was begun, together with intensive physiotherapy and postural drainage. A Gram-film of the sputum showed a profuse number of polymorphs and Gram-negative bacilli morphologically resembling *Bacteroides* sp.

Within 48 hours anaerobic culture of the sputum grew *Bacteroides melaninogenicus* and a *Fusobacterium* species, both in numbers greater than 10^6 organisms/ml, both were susceptible to

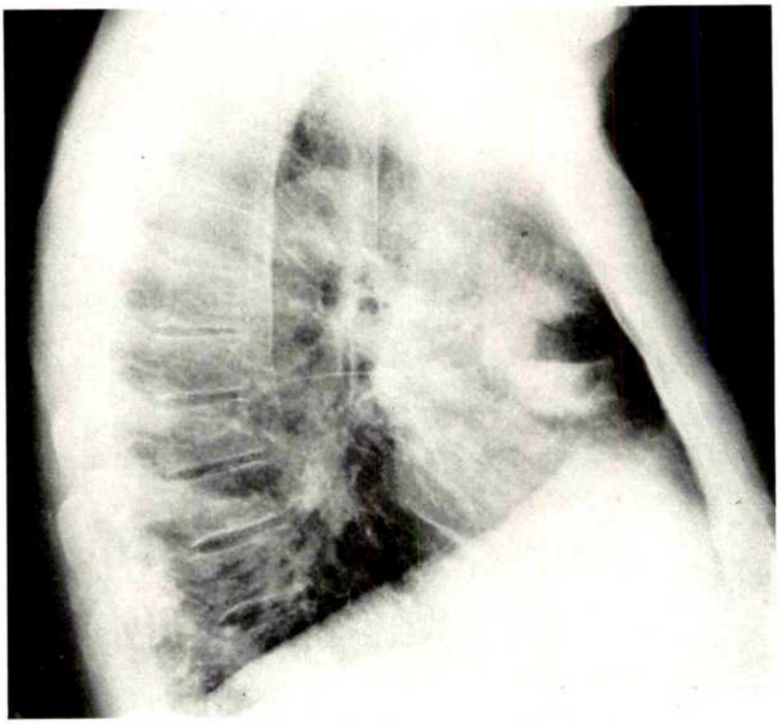

Fig. 4. Case 1. Lateral chest radiograph

ampicillin and metronidazole. The presence of anaerobic bacteria was also detected by the use of gas liquid chromatography (Fig. 1).

After 7 days treatment with metronidazole and ampicillin the patient remained feverish and with copious sputum. Ampicillin was then stopped and replaced by chloramphenicol 250 mg four times daily orally and the metronidazole was continued. Surgery was to be considered if the patient did not improve on this regimen. There was, however, a dramatic recovery after this combined treatment with marked decrease in the volume and odour of the sputum within 2–3 days.

Metronidazole was continued alone for a further 2 weeks, by which time the lung abscess had healed. The patient had no sputum and was discharged home. At follow-up 4 weeks later, the patient was symptom-free and chest radiograph revealed minimal fibrosis.

Case 2

Case 2 was a 25-year-old man found unconscious in his flat from an overdose of drugs, probably heroin. On admission he was found to have aspiration pneumonia of the right lung (Fig. 5). Initially he was treated with benzylpenicillin 2 mega units four times daily intravenously, gentamicin 80 mg three times daily intravenously and flucloxacillin 2 g four times daily intravenously together with naloxone hydrochloride, hydrocortisone and physiotherapy. His condition improved gradually and his chest radiograph began to clear. Gentamicin serum concentrations were closely monitored, adequate peak concentrations being achieved (6 μg/ml and 9 μg/ml) and no accumulation being detected (Noone & Rogers 1976).

Two weeks after admission he suddenly collapsed and became cyanosed and hypotensive. The chest radiograph showed an empyema (Fig. 6). He was resuscitated with intravenous fluid and hydrocortisone and an Argyll catheter was inserted into the empyema cavity. Foul-smelling pus was drained. Blood cultures taken at this time grew *Bacteroides fragilis*. Pus from the drain grew *B. fragilis*, anaerobic streptococci, *H. influenzae* and Group C β-haemolytic streptococci. The presence of anaerobic bacteria in the pus was also shown by the use of gas liquid chromatography

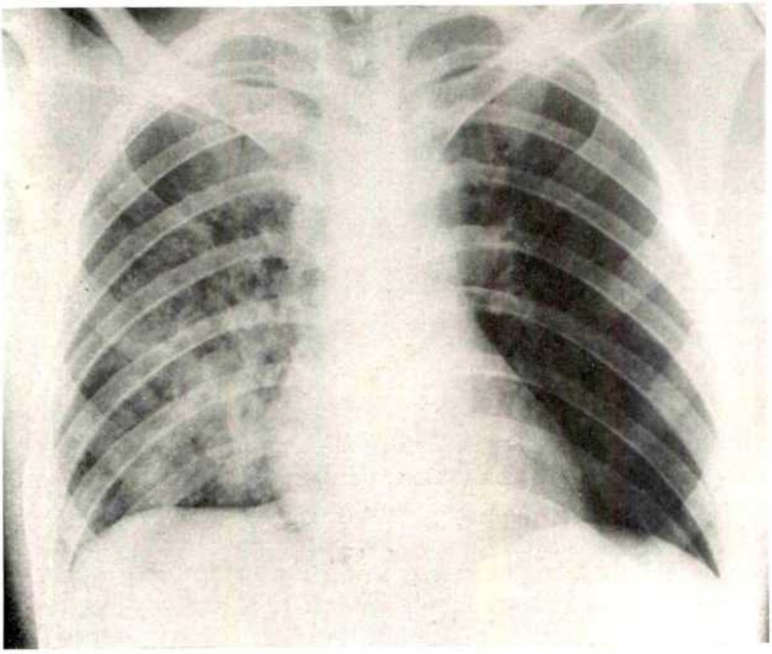

Fig. 5. Case 2. Chest radiograph showing aspiration pneumonia of the right lung

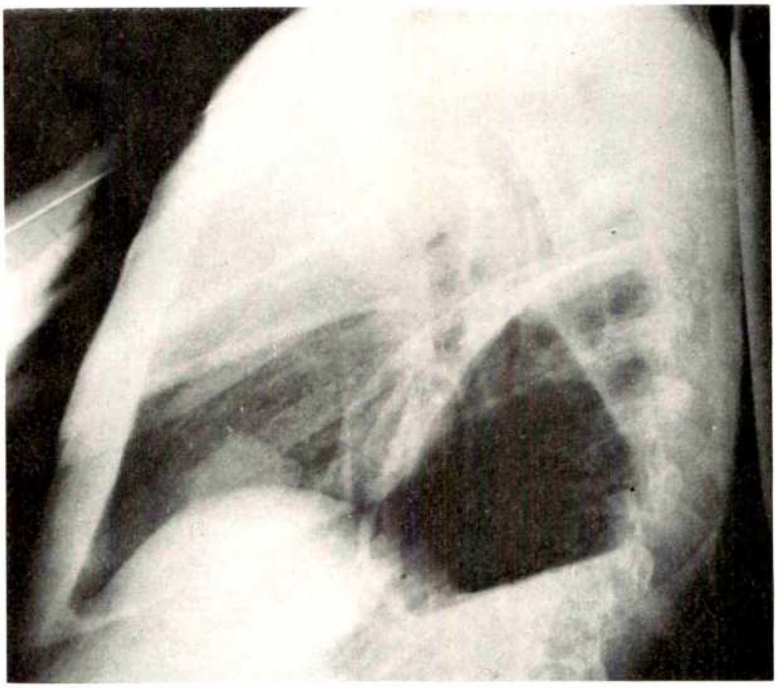

Fig. 6. Case 2. Lateral chest radiograph showing the posterior empyema cavity

(Fig. 2). Flucloxacillin and gentamicin were stopped and the patient was treated with oral metronidazole 800 mg three times daily and benzylpenicillin 1 g four times daily intravenously. He continued on these antibiotics with chest drainage for 4 weeks. The patient was discharged home well with no sputum, a fully expanded lung and normal respiratory function tests.

DISCUSSION

It seemed probable that both patients had aspiration pneumonia. This was suggested by the oral sepsis and history of vomiting of Case 1 and the unconscious state of Case 2 on admission. All three conditions predispose to aspiration. The site of their pneumonia (right-sided) is also suggestive of aspiration.

Both patients had a polymicrobial infection and non-sporing anaerobic bacteria were isolated in each case, both being common features of aspiration pneumonia (Bartlett et al. 1974). The strong clinical suspicion of anaerobic infections were rapidly confirmed by the use of gas–liquid chromatography to detect the presence of anaerobic bacteria in aspirated sputum and pus. Metronidazole and chloramphenicol cured Case 1. Case 2 was cured by chest drainage and a 4-week course of metronidazole and penicillin.

It is to be expected that non-sporing anaerobic bacteria such as *Bacteroides*, *Fusobacterium* and anaerobic streptococci will be incriminated as major pathogens in aspiration pneumonia because of their large numbers in the upper respiratory tract.

Recent clinical reports of pleuropulmonary infection (Bartlett & Finegold 1974) by anaerobic bacteria emphasize that infection with these pathogens within the thorax may present as pneumonia, pulmonary abscess, necrotizing pneumonia, septic emboli or empyema. Predisposing factors appear to be oral or nasopharyngeal sepsis, loss of consciousness, dysphagia and vomiting. Other predisposing factors include obstructive lesions associated with carcinoma or foreign bodies, metastatic spread of anaerobic infection outside the chest (usually from a pelvic or abdominal abscess), underlying diseases such as diabetes mellitus or malignancy, and treatment with steroids or immunosuppressants. Anaerobic infection should be suspected under these conditions. However, anaerobic pathogens virtually always occur in mixed infection, either with other anaerobic bacteria or with aerobic organisms. Isolation of aerobes does not automatically rule out the possibility of coincidental infection with anaerobes. Foul-smelling sputum or empyema fluid should also alert the clinicians to request the laboratory to carry out anaerobic culture and gas–liquid chromatography studies (if available). Specimens of empyema fluid, sputum samples and blood cultures should be examined. If the patient is intubated, has a tracheostomy or is examined by bronchoscopy sputum can be obtained by direct aspiration. Although there are advocates for transtracheal aspiration of sputum, this would seem to be unnecessarily hazardous for the patient.

Treatment of infections with non-sporing anaerobic bacteria has been surgical drainage with evacuation of pus when indicated, and appropriate antibiotic therapy. Most anaerobic bacteria in the upper respiratory tract are susceptible to benzylpenicillin as well as clindamycin. Both these drugs have been used extensively in the USA for the treatment of pulmonary infections caused by non-sporing anaerobic bacteria (Bartlett et al. 1975) with a cure rate of 75% and 84% respectively. Benzylpenicillin and ampicillin are effective against most non-sporing anaerobic bacteria causing lung infection, with the important exception of *B. fragilis*. The latter was isolated from Case 2 and was resistant to these penicillins. In many strains of *B. fragilis* this resistance is related to the production of β-lactamase (Pinkus et al. 1968; Editorial, *Lancet* 1973).

Clindamycin and lincomycin which are also active against *B. fragilis* have been used widely to treat non-sporing anaerobic infections during the last 5 years. Because of the not infrequent reports of pseudomembraneous colitis (Tedesco et al. 1974), which is associated with severe morbidity and considerable mortality, there has been a marked decline in the use of these two drugs.

Chloramphenicol is effective against most non-sporing anaerobic bacteria (Martin et al. 1972). Many clinicians are cautious about its use because of its potential toxic effect on the bone marrow. In life-threatening sepsis its advantages outweigh this risk.

Metronidazole is used in the treatment of trichomoniasis (Cosar & Joclon 1959), giardiasis (Bassily et al. 1970) and amoebiasis (Powell et al. 1969). More recently, it has been found to be an effective bactericidal agent against the great majority of anaerobic bacteria including *Bacteroides fragilis* (Tally et al. 1972, 1975; Luton Study Group 1974; Ingham 1975; Whelan & Hale 1973). Metronidazole diffuses well into tissue spaces and also crosses the blood–brain barrier (Tally et al. 1972). Successful results in the prophylaxis of infections due to non-sporing anaerobic bacteria have been obtained by several groups including the Luton Study Group (1974).

Metronidazole has minimal side effects which include metallic taste, a reversible sensory neuropathy after prolonged use (Drug and Therapeutics Bulletin 1976) and antabuse effect with alcohol (Merry & Whitehead 1968). It is well tolerated by most patients and is now replacing clindamycin and lincomycin as a first-line drug in the treatment of infection due to non-sporing anaerobic bacteria in many hospitals. Intravenous and suppository presentations of the drug are available for those patients unable to take the oral product (at present the intravenous preparation is under trial).

ACKNOWLEDGEMENTS

We would like to thank Dr Nigel Compston, under whose care the patients were admitted, for his cooperation with this paper. We also thank Mr Brian Farrell and the technical staff of the Microbiology Department for their help and Miss Susan Brassett for the typing.

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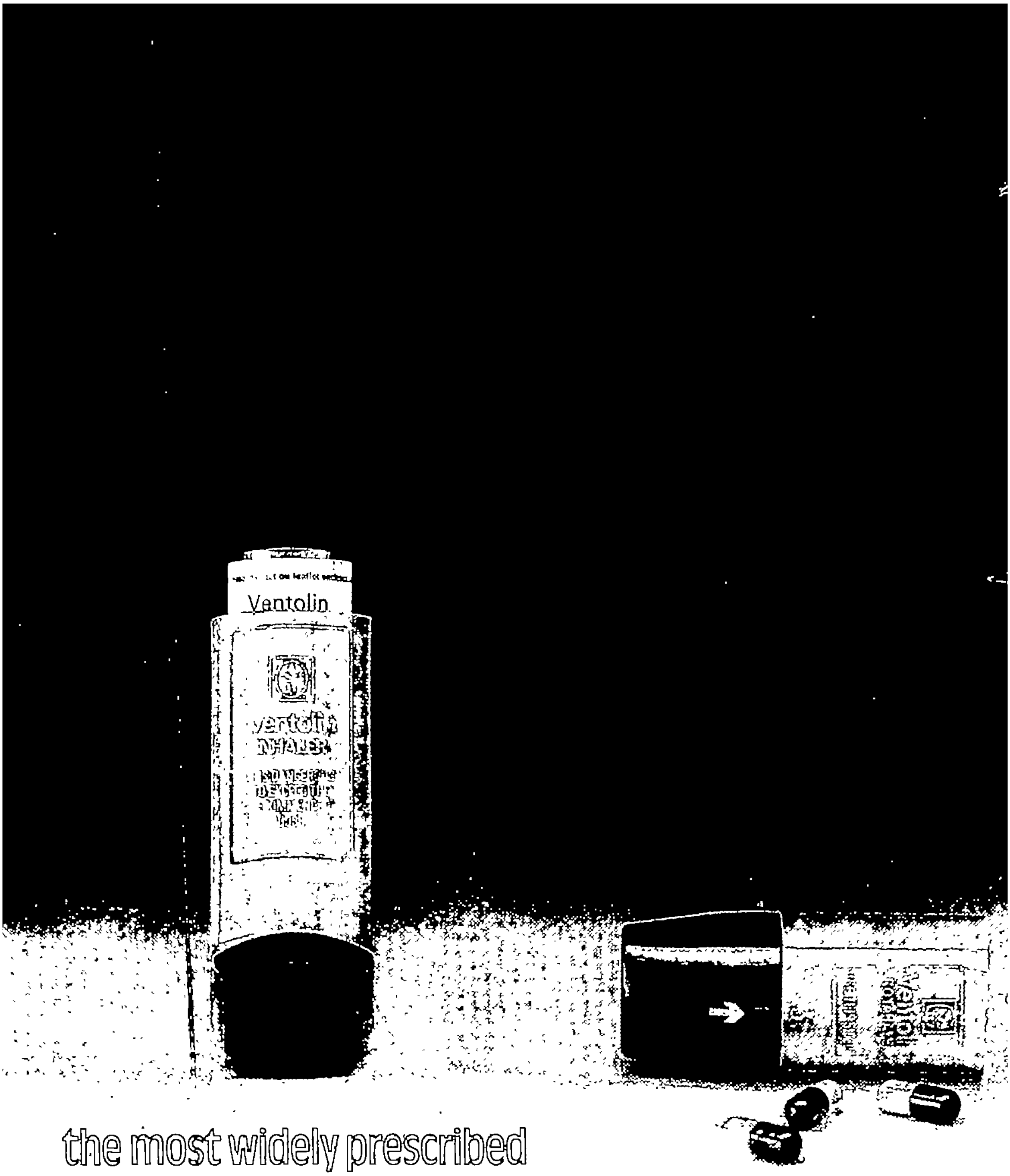

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Br. J. Dis. Chest (1978) 72, 196

HIGH-ALTITUDE ACCLIMATIZATION AND PROTEINURIA IN EAST AFRICA

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Summary

Seven climbers spent 6 weeks in the East African mountains, at heights of up to 5890 m. The mean protein urine concentration in morning specimens was over 100 mg/100 ml after climbs during the first 12 days but fell to 15 mg/100 ml during subsequent climbs. The highest concentrations (100–300 mg/100 ml) were in 5 climbers with peripheral oedema, 3 with obvious high-altitude illness. The findings implicate the kidney in high altitude acclimatization and illness.

INTRODUCTION

Proteinuria is part of the body's response to high altitude (Rennie & Joseph 1970) and suggests that hypoxaemia disturbs renal function (Rennie & Joseph 1970; Pines 1972). My study confirms this among the mountains of East Africa where high-altitude illness is very common. It shows that proteinuria greatly diminishes with repeated exposure to heights and that heavy excretion of protein may accompany high altitude illness.

Methods

Seven very experienced climbers spent 6 weeks in the Ruwenzori, Kilimanjaro and Kenya mountain areas (5110 m, 5890 m and 5200 m high). All had been to such heights before. From the start of the expedition, the first morning urine provided by each climber was tested daily for protein concentration, blood, glucose, ketones and pH, using reagent strips (Bili-Labstix). The bladder was emptied completely each night before bed. Reagent strips were dipped into urine immediately after voiding and read in a good light. A trace of protein was regarded arbitrarily as 15 mg/100 ml and higher amounts estimated according to the standard colour chart provided. This method of estimation is obviously crude, but is convenient in the field and avoids the inevitable deterioration if samples are transported in tropical conditions to a hospital laboratory. The specific gravity was measured by a clinical urinometer. Heights were measured by a Thommen's pocket altimeter and corrected by reference to published heights.

RESULTS

Fig. 1 shows the mean protein concentration daily, plotted against the heights where climbers camped each night. The crosses show the heights achieved during five climbs. Clearly there was marked proteinuria during the first two climbs but the remaining three climbs provoked little proteinuria during the 12th to the 33rd days. The pH of urine taken at 3000 m and higher was constantly 6, showing the alkalosis induced by height and which can affect protein strip reactions. This possible error was excluded by (*a*) disappearance of protein later despite constant alkalosis and (*b*) occasional tests with salicyl sulphonic acid which gave similar results.

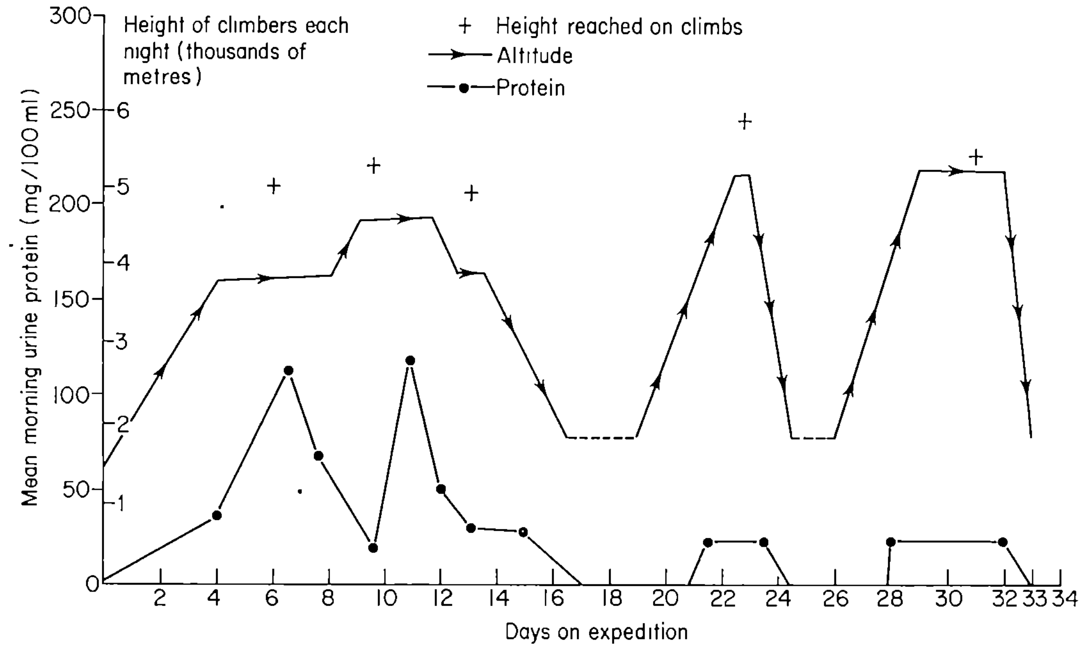

Fig. 1. Comparison of height and proteinuria during 33 consecutive days of the expedition

Only during the first climb were traces of blood and ketones found in three climbers During the period of the first two climbs, three men were prostrated with a single attack of high-altitude illness (severe malaise, nausea, oedema of the face, hands and feet and late inspiratory crackles) (Nath & Capel 1974). Small amounts of urine of high specific gravity were passed containing 100+ to 300 mg of protein/100 ml. Two others had an episode of pitting oedema of the face and hands but felt well; their urine was dilute but contained 100+ and 300 mg of protein/100 ml. The remaining fit climbers had proteinuria of 30–100 (mean 80) mg/100 ml in dilute urine (9 of 14 climbing attempts). Ratios of protein content and specific gravity were calculated to allow for dilutional effects but the results were not significantly affected.

DISCUSSION

Clearly proteinuria is an aspect of acclimatization to heights of 3000 m or more. Such proteinuria has been described at similar heights in the Himalayas (Rennie & Joseph 1970; Pines 1972). Over a period of 25 days at height, Rennie and Joseph thought that proteinuria persisted but diminished slightly. With intermittent exposure to heights and over the longer period described, I have shown that the protein greatly diminishes though it persists, as Rennie et al. (1971, 1972) found in altitude laboratory studies up to 5400 metres. This suggests that the kidney (as well as the rest of the body) has adapted to height and to relative hypoxaemia. Proteinuria was a definite response to height and not to exercise, for the most strenuous and exhausting periods of the trip were at heights up to 3000 m due to the very boggy and intensely, though exotically, vegetated ground.

The last of the climbs was on Mount Kenya, technically the most difficult and over 3 days with blizzards and cold bivouacs, but there was little proteinuria. An accompanying unacclimatized climber showed protein of 300 mg/100 ml during this climb with oliguria and malaise. Proteinuria due to exercise has usually disappeared from the next morning's urine (Rennie & Joseph 1970).

The heaviest proteinuria was in three climbers with high altitude illness and oedema and in two others with peripheral oedema only. At heights of 3000 m or more, renal plasma flow and filtration rate decrease (Monge et al. 1969) as does creatinine clearance (Rennie & Joseph 1970; Rennie et al. 1972; Epstein & Saruta 1972); aldosterone secretion drops remarkably (Slater et al. 1969; Pines et al. 1977) though for unknown reasons. These features suggest that alterations of kidney function play a part in acclimatization and in high-altitude illness, though the cause of these alterations and the excessive protein excretion remains obscure.

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ADDENDUM

These investigations were repeated during an 8-man expedition to Nanda Devi (7816 m) in the Gharwal Himalayas in 1977. They were performed during the approach march of 2 weeks and at lower camps on the mountain, at heights varying between 3500 and 6000 m. The same phenomena were found: marked proteinuria during earlier climbs to heights, diminishing with repeated ascents. Proteinuria was highest in 3 climbers who developed high-altitude illness and in whom showers of late inspiratory crackles were heard.

Br. J. Dis. Chest (1978) 72, 199

USE OF EXERCISE CHALLENGE TO INVESTIGATE POSSIBLE TOLERANCE TO BETA-ADRENOCEPTOR STIMULATION IN ASTHMA

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Summary

The effect of prolonged salbutamol administration on beta-adrenoceptor function in asthma has been examined. Six adult patients received salbutamol tablets (16 mg daily) for between 4 and 20 weeks and six adolescents received salbutamol aerosol (800 μg daily) for 2–5 weeks. Before and after the treatment period the acute bronchodilator response to inhaled salbutamol and the ability of inhaled salbutamol to protect against exercise-induced asthma were examined. Lymphocyte beta-adrenoceptor function was also measured in the patients on tablet therapy. Inhaled salbutamol was less effective in protecting against exercise-induced asthma at the end of the treatment period in the patients who had received tablet therapy, but otherwise there was no significant change in beta-receptor function of either airways or lymphocytes. This apparent loss of efficacy of inhaled salbutamol in the prevention of exercise-induced asthma in some subjects, even when its acute bronchodilator effect is preserved, might reflect differences in the susceptibility of different beta-adrenoceptors to desensitization after prolonged stimulation: its clinical importance remains uncertain.

INTRODUCTION

Although β sympathomimetic bronchodilators are widely used in the treatment of asthma, a clinical impression persists that their potency declines with time. Such tachyphylaxis can readily be demonstrated for the cardiovascular, muscle or metabolic effects of sympathetic stimulation (Conolly et al. 1971; Nelson 1973) but it has been more difficult to study the effects on the airways in asthma because of the innate variability of airway function and the inaccessibility of the relevant β-receptors. Studies of the bronchodilator response to β sympathomimetic agents after a period of conventional dosage have produced conflicting results (Formgren 1971; Gibson et al 1972; Jenne et al. 1975; Holgate & Tattersfield 1976; Svedmyr et al. 1976; Wilson et al. 1976). Prolonged stimulation by β sympathomimetic agents renders experimental animals more liable to bronchoconstriction induced by histamine or antigen challenge (Conolly et al. 1971; Izard et al. 1971; Bouhuys et al. 1972) but no comparable studies have been reported in asthma in man.

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Since β-receptors in the airways are difficult to study in vivo, several investigators have used, as a model, the β_2 adrenoceptor of peripheral blood lymphocytes, measuring changes in cyclic AMP levels produced by stimulation with isoprenaline in vitro. With this technique some studies (Logsdon et al. 1972; Parker & Smith 1973; Alston et al. 1974) have shown depressed β-receptor function in patients with asthma but others (Gillespie et al. 1974) have not. Conolly and Greenacre (1976), however, demonstrated that excessive use of adrenergic bronchodilators resulted in desensitization of the lymphocyte β-adrenoceptors while in comparable patients treated exclusively with non-adrenergic drugs desensitization was not found and this might explain the discrepancies.

In the present study we have re-examined possible tachyphylaxis to the effects of a selective β_2 stimulant (salbutamol) in a group of asthmatic patients. We investigated the effects of a period of treatment not only on base-line function and acute bronchodilator response but also on protection against an asthma-provoking stimulus. Exercise was chosen as the challenging stimulus because of its safety, convenience and reproducibility (Anderson et al. 1975). Additionally in some of the patients we studied β_2-receptor function of the lymphocytes to investigate whether changes after a period of treatment correlated with any tachyphylaxis of airway function.

Subjects and Methods

Twelve adolescent and young adult patients were studied (Table I). None was taking regular bronchodilators, though patients were not excluded if taking occasional bronchodilator by aerosol (not more than 200 μg salbutamol/day on average). Studies in any one subject were performed at the same time of day on each occasion (usually morning). Before exercise, peak expiratory flow rate (PEF) was measured using a Wright meter and two puffs of a placebo inhaler were administered. PEF was repeated after 10 min and the subject then performed a standard exercise test on a treadmill (Connolly & Godfrey 1970); each subject ran for a period of 6 min at a

Table I. Details of patients and of route, dose and duration of salbutamol therapy

Case	*Sex*	*Age*	*Duration* (weeks)
Oral salbutamol, 4 mg four times daily			
1	M	20	4
2	M	23	6
3	M	36	4
4	M	20	8
5	M	29	20
6	M	22	4
Inhaled salbutamol 200 μg four times daily			
7	F	14	3
8	F	15	3
9	M	16	4
10	F	13	4
11	M	14	5
12	M	14	2

speed and incline which raised the heart rate to at least 160 beats/min. During exercise, immediately afterwards, and at 1, 3 and 5 min, and every 5 min thereafter for a further 25 min, measurements of PEF were made. For each measurement the best of three PEF values was recorded, and for assessing the response to exercise the lowest recorded post-exercise value was used (this usually occurred between 3 and 10 min after the end of exercise). The values of PEF in each patient were expressed as a percentage of the value predicted from the patient's age, sex and height (Godfrey et al. 1970; Cotes 1975). After resting for 2 hours the procedure was repeated with two puffs of salbutamol (200 μg) substituted for the placebo aerosol. The nature of the aerosols was known to the investigator but not to the patients. To assess the efficacy of salbutamol the following indices were calculated:

$$\text{Degree of bronchodilation} = \frac{\text{PEF after active inhaler} - \text{PEF before}}{\text{predicted normal PEF}} \times 100$$

$$\text{\% fall of PEF on exercise} = \frac{\text{pre-exercise PEF} - \text{lowest post-exercise PEF}}{\text{pre-exercise PEF}} \times 100$$

$$\text{\% protection from exercise-induced asthma (EIA)} = \frac{\text{\% fall of PEF after placebo and exercise} - \text{\% fall after salbutamol and exercise}}{\text{\% fall after placebo and exercise}} \times 100$$

In the six adult patients (Cases 1–6) duplicate specimens of 60 ml venous blood were taken on separate days around the time of each study; β-receptor function of the lymphocytes was measured and the results analysed as described by Conolly and Greenacre (1977).

After the initial exercise and blood studies, the six adult patients were treated with salbutamol tablets in a dose of 4 mg four times daily, and the six adolescent patients were treated with regular inhaled salbutamol in a dose of 200 μg (two puffs) four times daily (Table I). The patients on tablet therapy were treated for between 4 and 8 weeks except for Case 5 in whom repeat exercise testing could not be performed until 20 weeks because of troublesome asthma. The treatment period in the patients on inhaled salbutamol varied between 2 and 5 weeks. At the end of the period of treatment the same exercise challenge and lymphocyte studies were repeated. Treatment was omitted for 8–12 hours before the repeat studies to avoid interference with the assessment of the effects of acute exposure to salbutamol.

The values for basal and maximum PEF and for bronchodilation were compared before and after the treatment period by paired *t*-test, and the exercise measurements (which were expressed as percentages) were transformed to the arc sin value of their square roots, in which form paired *t*-tests were carried out (Armitage 1971). In the six patients in whom lymphocyte studies were performed any possible correlation between changes in airway function and in lymphocyte β-receptor function was examined by least squares regression analysis.

Results

The only statistically significant difference ($P < 0.05$) apparent after the treatment period was a reduction in the protective effect of inhaled salbutamol against EIA in the patients who had been treated with salbutamol tablets (Fig. 1). There were also downward trends in the base-line and maximum PEF at rest but the bronchodilator response to inhaled salbutamol was preserved. There were no significant alterations in the group on inhaled salbutamol although similar trends were apparent (Fig. 2).

The response of the lymphocyte beta-adrenoceptors is shown in Fig. 3. There was no significant difference between the responses before and after the treatment period. Within individual patients no significant correlation was found between changes in the indices of bronchial and lymphocyte beta-adrenoceptor function.

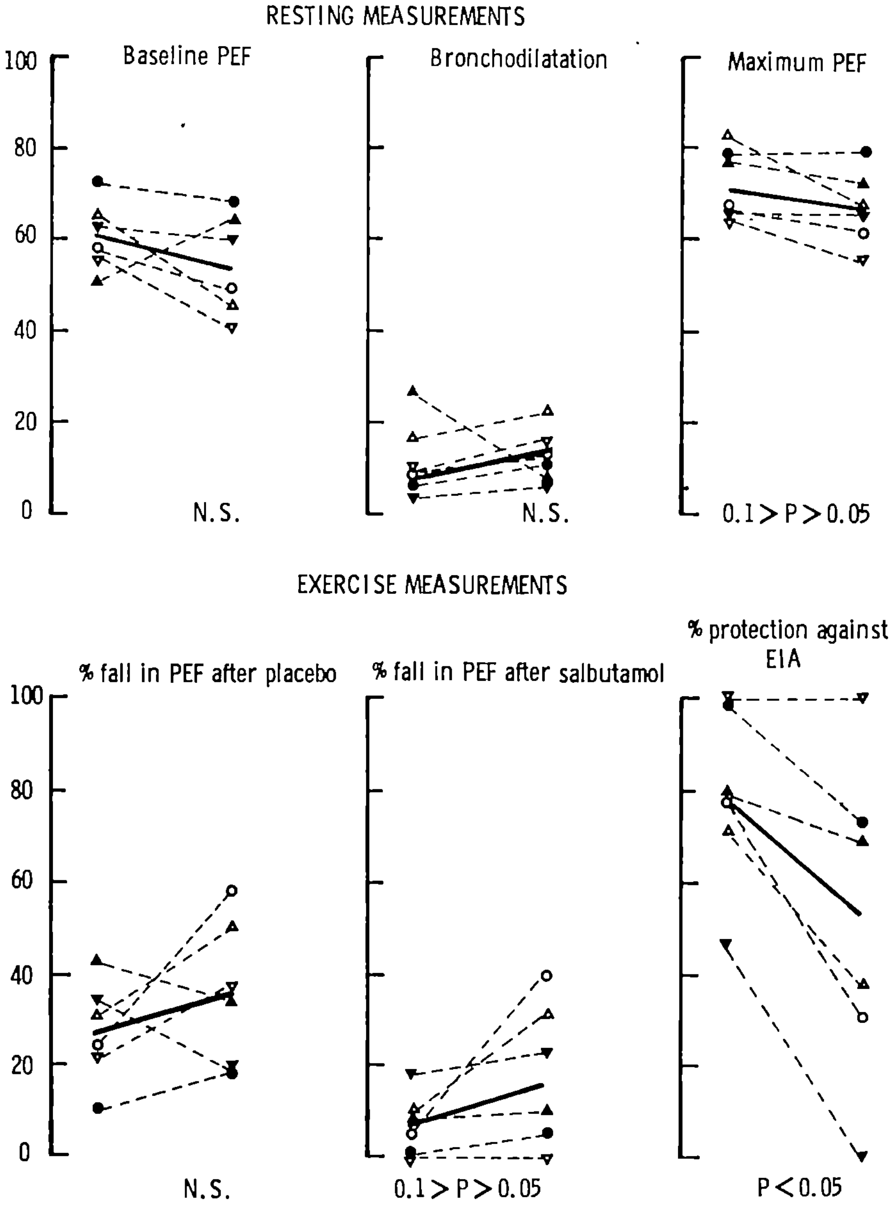

Fig. 1. Measurements of airway function in six patients before and after treatment with salbutamol tablets. Broken lines indicate results in individual patients and solid lines mean data. Upper three panels show measurements at rest; values of PEF on ordinate expressed as percentage of predicted value. Lower three panels show effects of exercise; ordinate represents percentage change in PEF compared with pre-exercise value in each study. ● Case 1; ▲ Case 2; ○ Case 3; △ Case 4; ▼ Case 5; ▽ Case 6

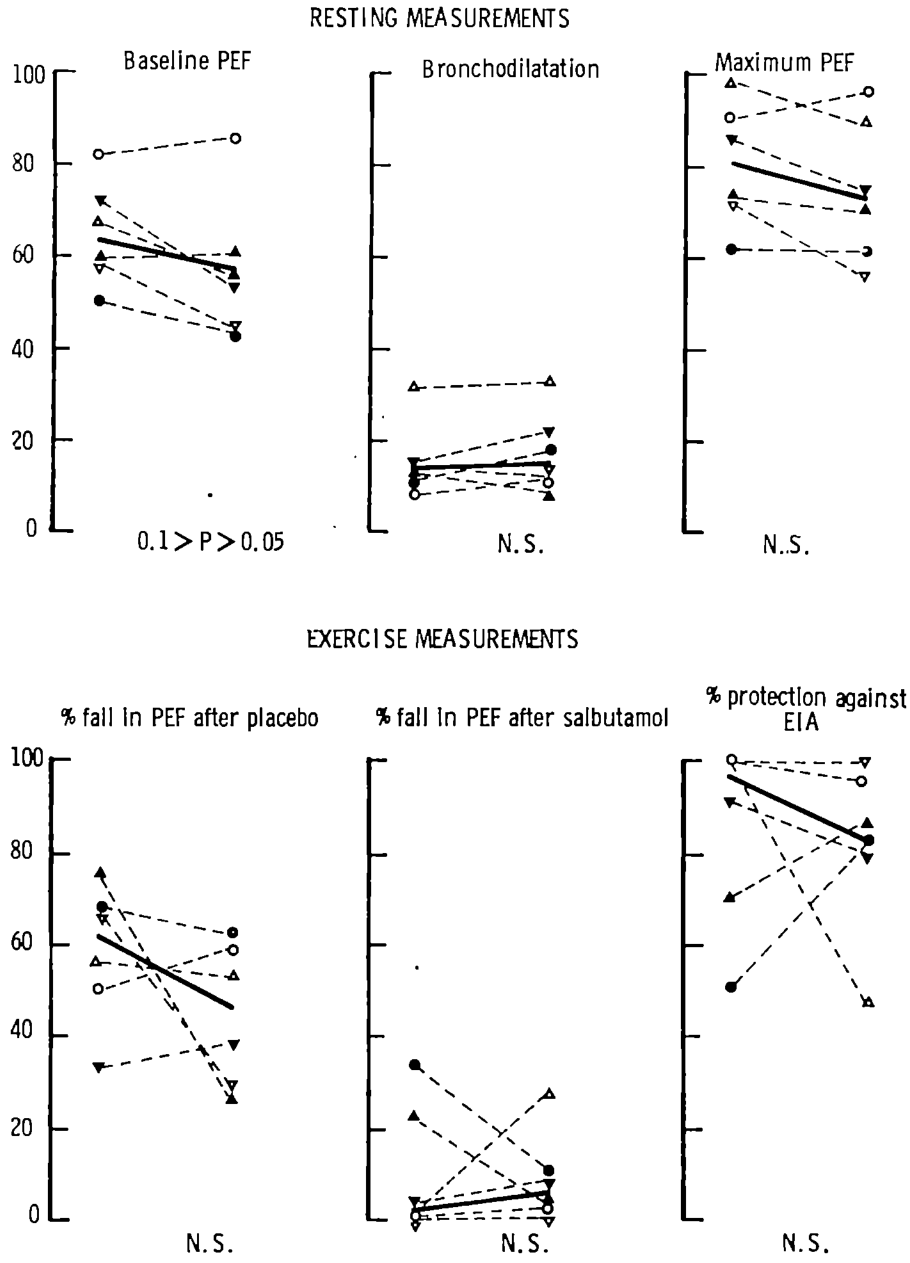

Fig. 2. Measurements of airway function in six patients before and after treatment with inhaled salbutamol. Presentation of data as in Fig. 1. ● Case 7; ▲ Case 8; ○ Case 9; △ Case 10; ▼ Case 11; ▽ Case 12

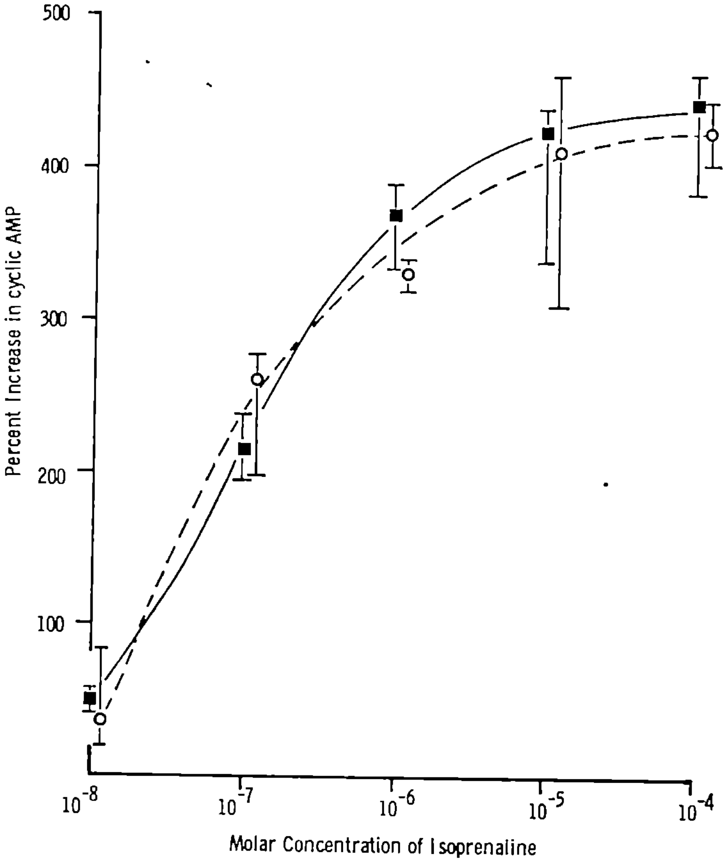

Fig. 3. Increase in cyclic AMP in lymphocytes in response to isoprenaline. Lymphocytes taken from six patients before (■) and after (○) treatment with salbutamol tablets. Response to each concentration of isoprenaline is plotted as the median ± interquartile range

Discussion

Our results suggest little overall change in β-receptor function of either airways or lymphocytes after treatment with salbutamol. The only significant change was a small reduction in the protection afforded against exercise-induced asthma in the patients treated with salbutamol tablets. Despite this apparent loss of effect, inhaled salbutamol retained its bronchodilator properties at the end of the study. A comparable dissociation between the bronchodilator properties of salbutamol and its efficacy in preventing exercise-induced asthma was noted by Anderson et al. (1976), suggesting differences between the β-receptors on bronchial smooth muscle and on mast cells. In general β-receptor resistance has proved more difficult to demonstrate in the airways than in other organs, and differences probably exist in the susceptibility to tachyphylaxis of different populations of beta-adrenoceptors. Furthermore Davis and Conolly (1977) have shown in vitro that human bronchial muscle from different individuals varies widely in its susceptibility to β-receptor tachyphylaxis.

No evidence of loss of activity of salbutamol was found in the patients treated by inhalation. The daily dose in these patients was naturally considerably lower, but the local dose in the airways is probably at least comparable; the patients were, however, younger and their mean treatment period was, on average, shorter.

Greenacre and Conolly (1978) found previously that similar doses of oral salbutamol produced some desensitization of lymphocyte β_2-adrenoceptors in normal subjects studied immediately after a period of prolonged therapy. Our failure to demonstrate a similar effect in the present study may indicate that some recovery of lymphocyte receptor response took place during the 8–12 hour period between the last dose of salbutamol and blood sampling.

The difficult question whether clinically important resistance to β-receptor stimulants develops in the bronchi with usual dosage is therefore still unanswered. Exacerbations of asthma have been observed during prolonged infusions of isoprenaline without corticosteroid cover (Paterson et al. 1971) and earlier observations (Keighley 1966; van Metre 1969) suggest that in some patients drug-induced resistance may be a significant problem. Holgate and Tattersfield (1976) have recently shown in normal subjects that even with therapeutic doses of inhaled salbutamol the increase in specific airway conductance produced acutely by salbutamol declines with regular exposure, and that this loss of response can be restored by systemic corticosteroids. Whether the modest degree of receptor desensitization which we have found after oral treatment with 16 mg salbutamol/day is important in patients with asthma on long-term β-receptor stimulants remains open to question.

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IMMUNOLOGICAL ABNORMALITIES IN BRONCHIECTASIS WITH CHRONIC BRONCHIAL SUPPURATION

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Summary

Fifty-three patients with bronchiectasis (chronic bronchial suppuration) of unknown cause, in whom the chronic production of purulent sputum was the prominent clinical feature, were investigated for possible immunological abnormalities. They were compared with two control groups comprising 50 patients with chronic bronchitis and emphysema and 33 patients with bronchial asthma.

Forty-two patients with bronchiectasis (79%) had at least one abnormality of immunoglobulin, usually elevation of IgA, IgG or IgM. Eight patients had all three immunoglobulin levels raised and this was related to severity of disease. Similar increases in immunoglobulin levels were observed in the control groups, but the frequency and severity of these changes were significantly greater in the bronchiectasis patients. Two patients had IgA deficiency.

There was a very high prevalence of rheumatoid factor (52%) and an increased prevalence of antinuclear factor (10%) in the bronchiectasis patients compared with the control groups. The presence of these autoantibodies did not correlate closely with severity of disease.

Ten patients with bronchiectasis (19%) had one or more autoimmune disorders, and the association of severe bronchiectasis, Hashimoto's thyroiditis and pernicious anaemia in one patient is described in detail.

The immunoglobulin changes, high incidence of autoantibodies and association with autoimmune disorders raises the possibility that in some patients with bronchiectasis (chronic bronchial suppuration) of apparent unknown cause abnormal immune mechanisms may be important in causing or perpetuating the condition.

INTRODUCTION

In recent years various immunological abnormalities have been reported in several chronic lung diseases. These include changes in immunoglobulin levels in chronic bronchitis and emphysema (Biegel & Krumholz 1968) and cryptogenic fibrosing alveolitis (Hobbs & Turner-Warwick 1967), and the presence of autoantibodies in cryptogenic fibrosing alveolitis (Tomasi et al. 1962; Turner-Warwick & Doniach 1965), pneumoconiosis (Turner-Warwick & Parkes 1970; Lippmann et al. 1973) and chronic bronchitis (Bonomo et al. 1966).

Bronchiectasis comprises a heterogeneous group of conditions and its clinical features vary from a mild condition with minimal symptoms to a severe progressive chronic lung disorder. Many factors have been implicated in its development (Mallory 1947) especially chronic bronchial infection. Whether such infection is a primary cause of the disease or merely a consequence of bronchial dilatation has caused controversy in the past (Mallory 1947). The severe bronchiectasis which occurs in primary acquired hypogammaglobulinaemia and selective IgA deficiency may be considered as primarily due to infection arising in immune deficiency states.

The aim of the present study was to look for immunological abnormalities in selected patients with bronchiectasis (chronic bronchial suppuration) of apparent unknown cause in whom the chronic production of purulent sputum was the prominent clinical feature.

Patients

Fifty-three patients with bronchiectasis were studied (31 men and 22 women). The mean age of the patients was 47 years (range 15–76 years). The diagnosis was based on a history of cough productive of purulent sputum (10–100 ml/day) in all patients; coarse crackles usually localized to one or both lower lobes were present in 47 patients and 52 patients (98%) had an abnormal plain chest radiograph. Patients with bronchiectasis secondary to known congenital or mechanical factors, previous pulmonary tuberculosis, cystic fibrosis or allergic bronchopulmonary aspergillosis were excluded.

The abnormalities in the chest radiographs were gross cystic bronchiectasis in 10, honeycomb and patchy reticular shadowing in 33 and increased lung markings due to abnormal bronchial shadowing in 9 patients. If the triad of history, physical signs and abnormal plain chest radiograph is present it has been considered that a diagnosis of bronchiectasis can be made with confidence even in the absence of bronchograms (Wynn-Williams 1953). Moreover, Gudbjerg (1957) in a review of 112 cases of bronchiectasis noted abnormalities of the plain chest radiograph in 93%. Because of these observations and to avoid unnecessary inconvenience to patients, bronchograms were not done routinely, although of the present series 11 patients had had bronchograms in the past which had confirmed the presence of bronchiectasis. Seven patients had had previous surgery and histology had confirmed bronchiectasis. Three patients died during the course of this study and autopsy confirmed the diagnosis of bronchiectasis. The duration of symptoms ranged from 1 to 74 years (mean 37).

The bronchiectasis patients were compared with two control groups. The first group consisted of 50 patients who had 'moderate' to 'severe' chronic bronchitis with FEV/VC$<55\%$ with absence of reversibility (39 men and 11 women). Their mean age was 63 years (range 45–78 years). The second control group included 33 patients with bronchial asthma (14 women and 19 men), average age was 49 years (range 15–69).

Clinical assessment of patients with bronchiectasis

A systematic history was obtained in all patients, recording the duration of sputum production, its colour and quantity, the presence of haemoptysis, possible precipitating factors, a family history of lung disease or autoimmune disease, the presence of joint symptoms, allergic disorder and details of cigarette-smoking. In addition to noting the abnormal physical findings of bronchiectasis, a general examination for clinical evidence of joint disease or autoimmune disorders was performed. Classification of patients into groups with mild, moderate or severe disease was made on the basis of clinical findings and radiographic changes.

Routine investigations included Hb, FBC and ESR; sputum examination for bacteria, fungi and eosinophils; urine examination for protein, cells and organisms; *Aspergillus* precipitins and prick skin tests to a variety of common allergens (house dust, house dust mite, mixed grass pollens, feathers; cat, horse and dog fur and *Aspergillus fumigatus*). Sweat electrolytes were measured in patients less than 30 years old.

Immunological investigations

Alpha-1 antitrypsin was measured by radial immunodiffusion using ICL Scientific immunoplates.

Immunoglobulins (IgA, IgG and IgM) were measured by radial immunodiffusion (ICL Scientific).

Complement (C3) was measured by radial immunodiffusion using Hyland immunoplates.

Autoantibodies

The presence of rheumatoid factor was determined by a latex slide method (Wellcome). Sera were examined for antibodies to nuclei, smooth muscle, mitochondria and parietal cells using standard indirect double layer immunofluorescent methods. A thyroid complement fixation test (Wellcome) was used to detect thyroid microsomal antibodies and both tanned red cell haemagglutination and latex slide agglutination tests (Wellcome) were used for detection of antibodies to human thyroglobulins.

RESULTS

Clinical assessment

Table I summarizes the clinical data from the 53 patients with bronchiectasis selected according to the above criteria. Twenty patients (38%) gave a history of a possible precipitating illness in childhood, adolescence or early adult life. This was described as 'bronchitis' (2), upper respiratory tract infection (2), scarlet fever (1) or pneumonia (15). No patient recalled measles or whooping cough as a preceding illness. The family history of lung disease noted in 22 patients was stated to be of 'bronchitis'. Although 26 patients had smoked cigarettes 15 of them had not smoked for more than 5 years and the majority of these had smoked less than 10 per day for a short time. Only 5 patients could be considered to have been heavy smokers (>20/day). Fourteen patients had joint symptoms, arthralgia in 10 and inflammary polyarthritis in four.

Table I. Summary of clinical data from 53 patients with bronchiectasis

	No. of patients
Precipitating illness	20 (38%)
Family history of lung disease	22 (41%)
Family history of allergy	8 (15%)
Family history of autoimmune disease	14 (26%)
Smokers	26 (49%)
Joint symptoms	14 (26%)
Atopic subjects	16 (30%)

Severity of disease

An attempt was made to devise an assessment of the severity of the disease on the basis of clinical features and radiographic changes. Twenty patients were considered to have severe disease on the criteria of production of more than 30 ml of purulent sputum daily, exertional dyspnoea, and radiological changes of cystic bronchiectasis or extensive honeycomb or reticular shadowing either bilaterally or throughout one lung. Twenty-six patients had moderately severe disease with 20–30 ml of purulent sputum daily, less dyspnoea and less extensive radiographic changes. Seven patients had mild disease (10–20 ml of purulent sputum daily, absence of dyspnoea and radiographic changes consisting of increased lung markings localised to one or both lower zones).

Routine investigations

The white cell count was raised in 7 patients by a polymorphonuclear leucocytosis. Sputum examination for eosinophils and fungi was negative in all patients. Bacteria were present in sputum from 27 patients (*H. influenzae* 20, coliforms 3, *Streptococcus pneumoniae* 3 and *Klebsiella aerogenes* 1). Urine examination was negative for protein, cells and organisms in all patients. *Aspergillus* precipitins were not detected in any of the sera. Sweat electrolytes were measured in 7 patients and were normal. On the basis of positive reactions to a variety of common allergens 16 patients were atopic. No evidence of α_1 antitrypsin deficiency was found.

Immunoglobulins

The normal range of values for our laboratory are IgA 1.5–4.0 g/litre, IgG 7–15 g/litre and IgM 0.5–1.5 g/litre.

Table II shows the frequency with which the levels of each of these immunoglobulins were raised in all groups studied. Elevation of all three immunoglobulin levels occurred in all of the chronic lung diseases studied but the frequency and degree of this increase was greatest in the bronchiectasis group. Patients with bronchiectasis had a raised IgA which was significantly greater than in both chronic bronchitis and asthma ($P < 0.025$). When chronic bronchitics were compared with asthmatics there was also a significant difference ($P < 0.05$). Similarly patients with bronchiectasis had a raised IgG significantly greater than those with chronic bronchitis and asthma ($P < 0.0005$) with no significant difference between the chronic bronchitis and asthma groups. For IgM the difference between the bronchiectasis patients and the control groups was also significant ($P < 0.0005$) but there was no significant difference between chronic bronchitis and asthma. Forty-two patients (79%) with bronchiectasis had at least one abnormality of immunoglobulin concentration.

Table II. Immunoglobulin levels in bronchiectasis, chronic bronchitis and asthma

	Bronchiectasis	*Chronic bronchitis and emphysema*	*Asthma*
Increased IgA	22 (41%)	15 (30%)	3 (9%)
Increased IgG	21 (40%)	10 (20%)	1 (3%)
Increased IgM	27 (51%)	7 (14%)	7 (21%)
Two Ig levels abnormal	15 (28%)	7 (14%)	1 (3%)
Three Ig levels abnormal	8 (15%)	—	—
Total number with abnormalities	42 (79%)	25 (50%)	10 (30%)

Number of patients tested: bronchiectasis 53, chronic bronchitis and emphysema 50, asthma 33.

In those patients with only one increased immunoglobulin level the most frequent abnormality was of IgM (10/14). Of the 8 patients with increases in all three immunoglobulin levels 6 had severe and 2 moderate disease.

Three patients had low IgA levels (0.3 g/litre, < 0.15 g/litre and nil respectively). The latter two patients fulfilled the criteria for selective IgA deficiency and these two patients also had associated autoimmune diseases (ulcerative colitis and pernicious anaemia).

Complement (C3)

The normal range for our laboratory is 1.2–1.65 g/litre.

Low C3 levels (mean 0.7 g/litre) were found in only one patient with bronchiectasis. The values in this patient were consistently low and were not related to exacerbations of the disease. This patient had moderately severe disease and no associated autoimmune disease.

Autoantibodies

Table III summarizes the incidence of rheumatoid factor and antinuclear factor in the bronchiectasis patients and the two control groups. There was a highly significant increased incidence of rheumatoid factor ($P < 0.0005$) in the bronchiectasis patients compared with the controls. The difference in incidence of rheumatoid factor between chronic bronchitis and bronchial asthma was not significant. The incidence of rheumatoid factor in the bronchial asthma group was only slightly above that of the normal population (4–5%). Because the mean age of the chronic bronchitis group was higher than the bronchiectasis group, this further emphasizes the difference because the prevalence of rheumatoid factor increases with age. The increased prevalence of antinuclear factor in bronchiectasis was also significant ($P < 0.013$). Twenty-five patients with bronchiectasis had rheumatoid factor with absence of antinuclear factor, three patients had antinuclear factor and only two patients had both antibodies. The presence of rheumatoid factor did not correlate closely with severity of disease in bronchiectasis. Of 27 patients with this rheumatoid factor 9 had severe, 13 moderate and 5 mild disease.

Table III. Prevalence of rheumatoid and antinuclear factors in bronchiectasis, chronic bronchitis and emphysema and asthma

	Bronchiectasis	*Chronic bronchitis and emphysema*	*Asthma*
Rheumatoid factor	27/52 (52%)	7/50 (14%)	2/33 (6%)
Antinuclear factor	5/50 (10%)	0/50	0/33
Mean age	47	63	49

Autoimmune diseases

Ten patients with bronchiectasis (19%) suffered also from one or more autoimmune diseases which are listed in Table IV. The occasional dramatic association between bronchiectasis and autoimmune disorders is illustrated by the following case history.

Table IV. Bronchiectasis-associated autoimmune diseases in 53 patients

	No. of patients
Hashimoto's thyroiditis and latent pernicious anaemia	1
Myxoedema (positive thyroid antibodies)	1
Coeliac disease	2
Ulcerative colitis (+IgA deficiency)	1
Rheumatoid arthritis	1
Systemic lupus erythematosus and diabetes mellitus	1
Primary biliary cirrhosis	1
Pernicious anaemia (+IgA deficiency)	1
Raynaud's phenomenon	1
Total	10

A 58-year-old woman (K.B.) developed cough with production of purulent sputum 25 years ago with no history of a precipitating or preceding illness. Within 5 years of onset of her illness extensive bronchiectasis had affected the right lung predominantly and bronchograms confirmed this diagnosis (Figs 1, 2). Two years later she had a right pneumonectomy and histological examination showed severe bronchiectasis with marked infiltration of the bronchial walls and peribronchial tissues with chronic inflammatory cells (lymphocytes and plasma cells). After a further 2 years she developed myxoedema and thyroid gland biopsy showed evidence of Hashimoto's thyroiditis; antithyroglobulin thyroid antibodies were present (1/2500). Four years ago a diagnosis of latent pernicious anaemia was made on the basis of a low serum B12 level, achlorhydria, positive Schilling test and the presence of parietal cell antibodies (1/8) in spite of a normal Hb. She has raised IgA and IgG levels and positive rheumatoid and antinuclear factors.

Two patients had adult coeliac disease. In both cases bronchiectasis preceded the symptoms of coeliac disease by several years. Two patients with an inflammatory polyarthritis had rheumatoid arthritis and systemic lupus erythematosus respectively. Again, in both cases, chest symptoms antedated the onset of the connective tissue disease. One patient was found to have mitochondrial antibodies. Liver function tests showed raised serum transaminases and alkaline phosphatase and a liver biopsy confirmed the presence of primary biliary cirrhosis.

DISCUSSION

The term bronchiectasis includes a variety of conditions of suspected or known cause in which dilatation of the bronchi is only one pathological feature. For the type of patient included in the present study it may be more appropriate to use the term chronic bronchial suppuration since the regular production of purulent sputum was the dominant symptom. Clinically and pathologically some of these patients resemble patients with bronchiectasis secondary to primary acquired hypogammaglobulinaemia where a clear immune deficiency predisposes to the disease.

In this study we have included 15 patients with a history of bronchopneumonia preceding the onset of their disorder. Although this is considered to be a cause of bronchiectasis, the relationship of illness in childhood to subsequent disease is often not clear and difficult to establish, and the majority of patients with acute bronchopneumonia do not experience long-term sequelae. The continuing long-term production of purulent

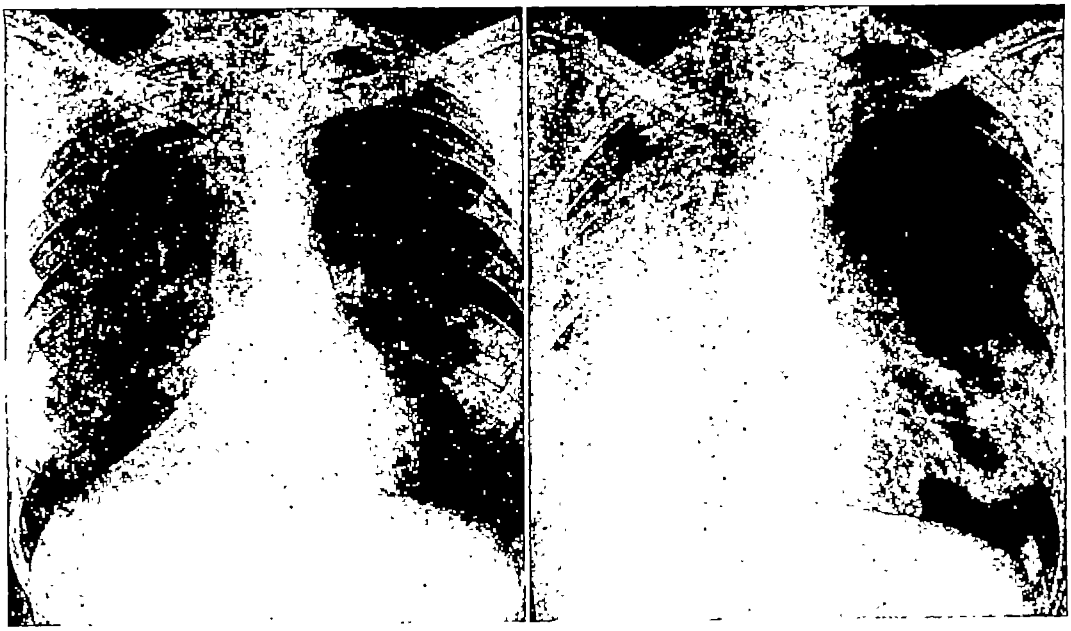

Fig. 1. Patient K.B. chest radiographs. *Left,* Initial radiograph with minimal changes. *Right,* Five years later, showing extensive bronchiectasis of the right lung

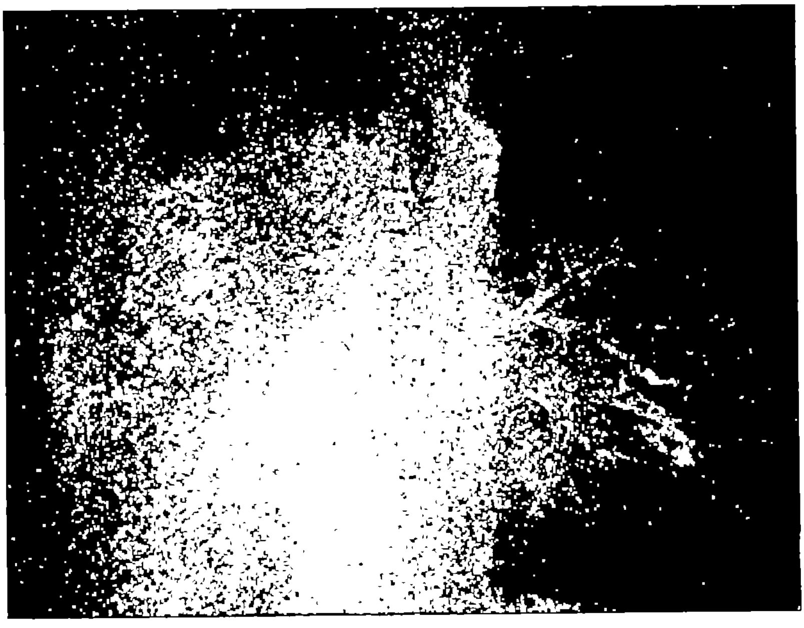

Fig. 2. Patient K.B. Bronchogram confirming severe bronchiectasis of the right lung

sputum in all our patients is more consistent with a persistent active inflammatory process than a simple mechanical cause. The presence of large numbers of acute and chronic inflammatory cells (lymphocytes and plasma cells) infiltrating the walls of dilated bronchi and bronchioles and the peribronchial tissues in lung tissue of those patients who had had surgery and from the three autopsy studies provides further evidence of this. Many earlier studies of the pathology of bronchiectasis have noted the presence of a destructive inflammatory process (Robinson 1933; Mallory 1947; Whitwell 1952).

The elevation of immunoglobulin levels demonstrated most frequently in the bronchiectasis patients probably represents a secondary response to persistent antigenic stimulation, and the very high incidence in our patients compared with the control groups may be explained by the selection of our patients on the basis of purulent sputum production. Similar immunoglobulin changes have been reported in cystic fibrosis (Schwartz 1966; Wallwork et al. 1974), recurrent bronchopulmonary infections (Kagan et al. 1975), chronic bronchitis and emphysema (Biegel & Krumholz 1968; Falk et al. 1970): conditions all characterized by purulent sputum production to a varying degree. With the exception of three patients with IgA deficiency, no quantitative change in immunoglobulins was found as a predisposing factor to the development of chronic bronchial suppuration.

Although it is known that low C3 levels may be associated with recurrent infections (Alper et al. 1972) the reduced C3 levels found in one patient may be due to activation of complement by circulating immune complexes. Further studies have shown that in some patients with chronic bronchial suppuration and other chronic lung diseases immune complexes are present in serum (Hilton et al. 1978).

The high incidence of rheumatoid factor and antinuclear factor in patients with chronic bronchial suppuration has also been reported in many other chronic lung diseases. These include conditions where production of purulent sputum is present such as cystic fibrosis (Høiby & Wiik 1975) and chronic bronchitis (Bonomo et al. 1966; Hodson & Turner-Warwick 1976) and also diseases in which infection is less prominent, as in cryptogenic fibrosing alveolitis (Turner-Warwick & Haslam 1971), asbestosis (Turner-Warwick & Parkes 1970) and coal miners' pneumoconiosis (Lippmann et al. 1973; Soutar et al. 1974). In addition to chronic lung disease rheumatoid factor may be present in many non-rheumatoid conditions and it has been established that it can be produced in response to immunization (Bartfeld 1969). In acute infections when the stimulus for their production has been removed rheumatoid factors disappear. Thus the persistent presence of rheumatoid factor in chronic disease suggests that its production is secondary to persistent antigenic stimulation, presumably by antigens derived from infective agents and/or products of tissue destruction. It has also been suggested that rheumatoid factor production may be evoked as a response to immune complex formation (Lurhuma et al. 1976). Although it is considered unlikely that antinuclear factors have a primary role in causing tissue damage (Turner-Warwick & Haslam 1971), it has been suggested that the presence of certain autoantibodies may enhance progression of disease in some patients with asbestosis (Turner-Warwick & Parkes 1970).

The high incidence of autoimmune disease in our patients with chronic bronchial suppuration was unexpected. Although two of the 10 patients had IgA deficiency which is known to be associated with autoimmune disease (Ammann & Hong 1971), the overall incidence is still high (15%). Walker (1967) reported an association between bronchiectasis and rheumatoid arthritis. The increased incidence of pulmonary disease in his study could not be explained by the greater susceptibility to infection of rheumatoid patients since the symptoms of bronchiectasis preceded those of arthritis in most cases. Similarly seven of our patients had bronchiectasis before the development of their autoimmune disease.

In our patient with severe bronchiectasis who later developed Hashimoto's thyroiditis and pernicious anaemia, it could be that her right lung was destroyed by an autoimmune process. This hypothesis is supported by the histological findings of large numbers of chronic inflammatory cells in the bronchial walls and peribronchial tissues, changes which characterize many organ-specific autoimmune diseases. Two patients with chronic bronchial suppuration later developed adult coeliac disease. An association between coeliac disease and fibrosing alveolitis was described by Lancaster-Smith et al. (1971) and cryptogenic fibrosing alveolitis has been shown to be associated with several other autoimmune disorders including rheumatoid arthritis, Sjogren's syndrome, chronic active hepatitis, Hashimoto's thyroiditis and pernicious anaemia (Turner-Warwick 1973).

Although cryptogenic fibrosing alveolitis and chronic bronchial suppuration are clinically and pathologically two separate diseases, this study has shown that some patients with chronic bronchial suppuration have immunological changes similar to those observed in some patients with fibrosing alveolitis.

The significance of the changes we have recorded is unknown. Although many of the observed phenomena are probably secondary to a chronic disease process, it is possible that abnormal immune mechanisms play a pathogenetic role in some patients with chronic bronchial suppuration. The immunological abnormalities observed in this study may be useful clinically to define a subgroup of patients with bronchiectasis in whom further investigation may identify a basic underlying defect in immunity.

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Case notes

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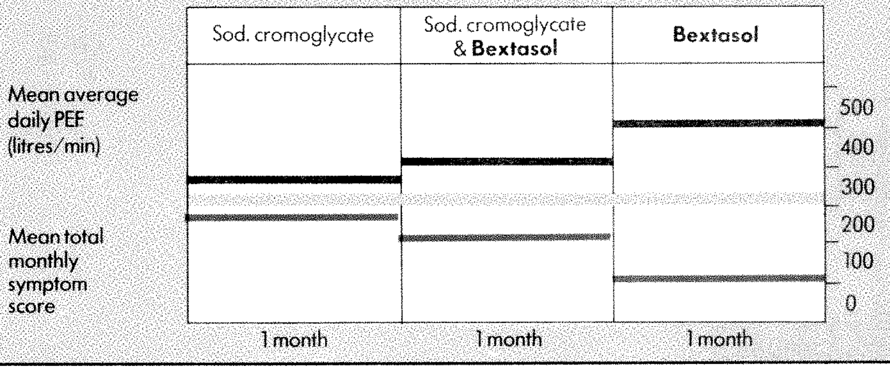

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References 1. *Practitioner* (1977) **218,** 128 2. *Practitioner* (1977) **218,** 856

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SHORT COURSE

Mynah

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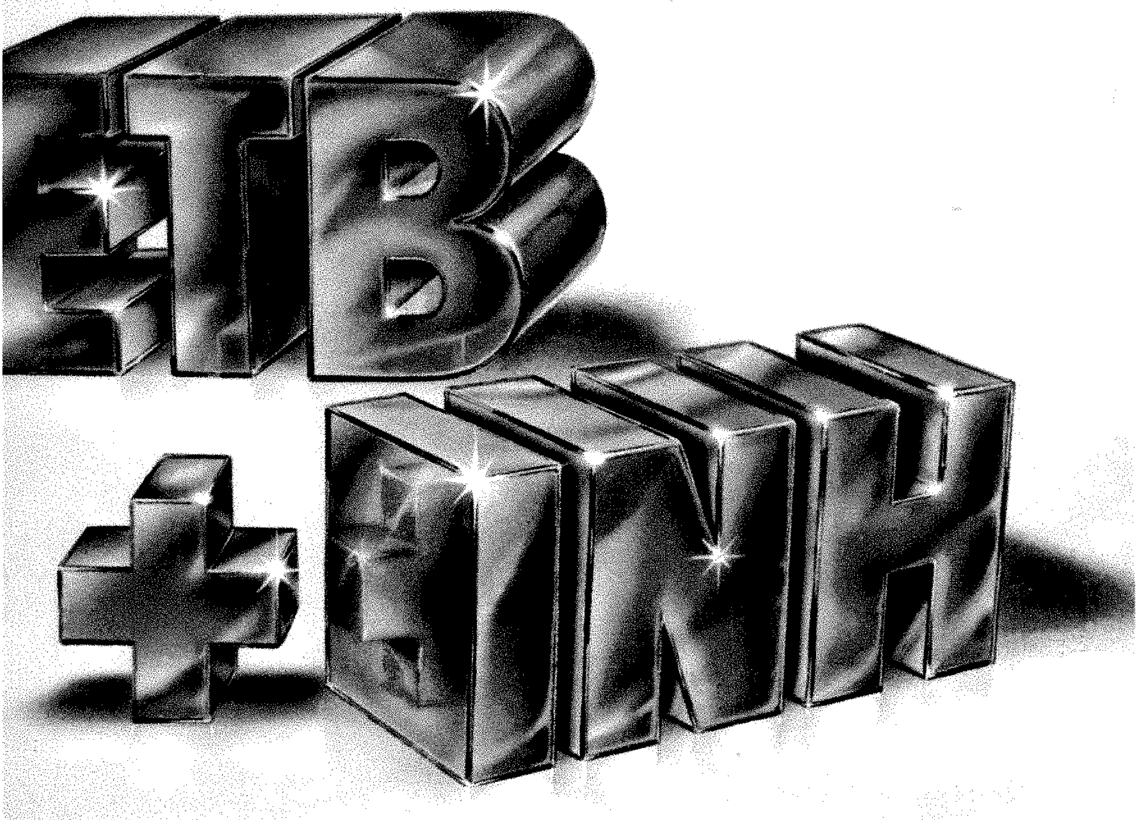

12 months' total treatment o tuberculosis with ethambut plus isoniazid

> ...six months' treatment with daily rifampicin plus isoniazid is of too short duration... treatment for one year or even nine months may be adequate.
>
> ...rifampicin is expensive, and it seemed possible that it might not be necessary to use it throughout treatment.
>
> ...since there were no relapses after a year's treatment whether continuation therapy was carried out with rifampicin plus isoniazi or with ethambutol plus isoniazid.
>
> Since the regimen of isoniazid, rifampicin and ethambutol followed by isoniazid and ethambutol proved uniformly successful we are no investigating the feasibility of shortening the total duration of treatment to nine months and giving rifampicin initially for two, three, or four months.

Lees A. W. et al, Lancet, 1977, 1232

Prescribing Information

Presentation: 1. Mynah 200. Each white tablet coded Lederle 5033 contains — 200 mg. Ethambutol plus 100 mg. Isoniazid. 2. Mynah 250. Each yellow tablet coded Lederle 5133 contains — 250 mg. Ethambutol plus 100 mg. Isoniazid. 3. Mynah 300. Each orange tablet coded Lederle 5137 contains — 300 mg. Ethambutol plus 100 mg. Isoniazid. 4. Mynah 365. Each pink tablet coded Lederle 5134 contains — 365 mg. Ethambutol plus 100 mg. Isoniazid. **Uses:** Mynah is a combination of two antitubercular drugs, for use in the primary treatment and re-treatment of tuberculosis especially when hypersensitivity or toxic reactions prevent the use of the other standard drugs. **Dosage and Administration:** (Adults only) Dosage of Mynah is gauged according to the patient's body weight, which governs the included amount of ethambutol; the dosage of isoniazid is standardised at 100 mg. per tablet. *For Primary Treatment:-* Mynah should be administered in a single daily oral dose such that the patient receives 15 mg./kg. of ethambutol plus 300 mg. isoniazid, concomitant drugs being used at their recommended dosage levels. *For re-treatment:-* For the first sixty days treatment, Mynah should be administered in a single daily oral dose such that the patient receives 25 mg./kg. of ethambutol plus 300 mg. of isoniazid, concomitant drugs being used at their recommended dosage levels. Thereafter proceed as in 'Primary Treatment' above. *NOTE* In order to obtain maximum effect due to high serum levels, drug administration should be once daily. Absorption is not significantly altered by administration with food. **Contra-indications, Warnings, etc.:** *Contra-indications:* Mynah is contra-indicated in patients who are known to be hypersensitive to ethambutol or isoniazid. It is also contra-indicated in patients with known optic neuritis unless clinical judgement determines that it may be used. Although no absolute contra-indications to the administration of isoniazid have been reported, care should be exercised in the administration of Mynah to epileptic patients since it may induce convulsions, and in the presence of impaired renal function. *Precautions:* Patients with decreased renal function may need to have the dosage adjusted as determined by blood levels of ethambutol. Animal studies with ethambutol have not demonstrated any teratogenic potential and there have been several reports of the drug having been administered during pregnancy without untoward effect. Nevertheless, it is recommended that the possibility of such effects should be kept in mind when treating women of childbearing age. Because ethambutol has a unique effect on the eye, it is recommended that patients undergo a full ophthalmic examination before starting treatment. This should include visual acuity, colour vision perimetry and ophthalmoscopy. Many physicians consider that routine ophthalmological examination is not thereafter necessary, but patients should be informed of the importance of reporting any change in vision. *Side effects:* FOR ETHAMBUTOL Ethambutol may produce a unique type of visual impairment which is generally reversible and which appears to be due to optic neuritis and to be related to dose and duration of treatment. Less than 1% of patients undergoing treatment with the higher dose regimen of 25 mg./kg./day for two months, and 15mg./kg./day thereafter, have exhibited decrease in visual acuity. The change may be unilateral or bilateral and hence both eyes must be tested individually. Recovery of visual acuity has usually occurred over a period of weeks to months after the drug was discontinued, and patients have then received ethambutol at lower dosages without toxicity. Test patients receiving ethambutol as sole therapy did not have gastro-intestinal disturbances (e.g. anorexia, nausea, vomiting, diarrhoea) transient impairment of liver function or allergic reactions, although these have been noted during antitubercular therapy in which ethambutol was employed. Numbness and paraesthesia of the extremities have been reported. FOR ISONIAZID. Side effects are infrequently encountered and are rarely serious. Peripheral neuritis is most often observed, and correlation exists between the dosage level and this reaction. When the dosage is 3 mg./kg./day, the incidence is approximately 1%; at 10 mg./kg./day, it rises to 15% or higher. Pyridoxine (Vit B6) has been used successfully for prophylaxis and treatment of isoniazid-induced peripheral neuritis. CNS effects (insomnia, headache, restlessness, mental confusion, toxic psychoses, increased reflexes, muscle twitching, paraesthesia) may be encountered. Optic neuritis and optic atrophy have been reported. Ophthalmological examinations should be carried out wherever visual complaints occur, since the optic lesions are likely to be reversible if isoniazid is discontinued promptly. Extremely high dosages have produced convulsions in apparently normal individuals. Urinary disturbances in the male (prostatic obstruction syndrome), constipation and dryness of the mouth have been reported. Allergic reactions occur infrequently. Hepatitis, agranulocytosis and exfoliative dermatitis have occasionally been reported. *Overdosage:* No specific antidote, but gastric lavage should be employed if necessary. **Pharmaceutical Precautions:** Mynah tablets should be stored at room temperature, in either the original pack or in containers which prevent access of light and air. **Legal Category:** T.S.A. **Further information:** Nil. **Product Licence Nos.:** Mynah 200. PLR 0095/5054. Mynah 250. PLR 0095/5055. Mynah 300. PLR 0095/5056. Mynah 365. PLR 0095/5057. **Package Quantities:** Mynah 200 : Bottles of 84. Mynah 250 : Bottles of 84. Mynah 300 : Bottles of 84. Mynah 365 : Bottles of 84. **Date of preparation or last review:** October 1975.

SHORT COURSE

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Br. J. Dis. Chest (1978) 72, 217

AN ASSESSMENT OF THE PLACE OF FOLLOW-UP IN PULMONARY TUBERCULOSIS

S. P. HAYDEN* AND V. H. SPRINGETT

East Birmingham Hospital, Birmingham

Summary

In 1971–4 forty-four patients were found to have drug-susceptible tubercle bacilli in their sputum more than one year after a previous positive result. Comparison of their case records with those of 45 controls showed that inadequate chemotherapy was by far the most important cause of relapse. Most patients who have had adequate chemotherapy for pulmonary tuberculosis should be discharged. Patients who have certain risk factors or who have had inadequate or irregular chemotherapy should be followed up indefinitely.

INTRODUCTION

Several studies have shown that the relapse rate in patients adequately treated for pulmonary tuberculosis is very low, probably less than 1% in patients observed for different periods of follow-up of several years duration (Thomas 1965; Pearce & Horne 1974). Springett (1971) found a relapse rate in the order of 1 per 1000 per year. Conversely, it has been shown that the most important cause of relapse is inadequate chemotherapy (Edsall et al. 1970; Bailey et al. 1973). It should, therefore, be possible to discharge from follow-up patients who have received adequate chemotherapy for pulmonary tuberculosis and this policy has been advocated (Leading Article, *Tubercle* 1973; British Thoracic and Tuberculosis Association 1975; Groth-Petersen 1976). In Birmingham in 1974, about 8000 patients were being followed up for pulmonary tuberculosis, of whom an estimated 5000 had received adequate chemotherapy. The remaining 3000 patients are being followed up for minimal lesions or from the pre-chemotherapy days. There is, therefore, scope for much saving of time for both staff and patients if adequately treated patients could be discharged from follow-up. We have investigated all cases of relapsed sputum-positive and chronic sputum-positive pulmonary tuberculosis in Birmingham in the years 1971–4 to determine (*a*) what factors are important in the causation of relapse and (*b*) how effective routine follow-up was in detecting relapse in patients with and without risk factors.

Patients and Methods

Two groups were studied:

1. A group of patients either relapsed or with chronic sputum positive.
2. A group of control patients.

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The relapsed and chronic sputum-positive group

These patients were identified from information supplied by the Public Health Laboratory Service, Birmingham. Relapsed patients were those who produced a positive sputum more than one year after sputum conversion. The chronic positive sputum state for the purposes of this investigation was one in which the sputum did not become negative by one year after initiation of chemotherapy. Sixteen patients in the relapsed and chronic positive sputum group had drug-resistant organisms. They were not included in this study because we feel they form a separate group and they are the subject of another study (Thomas 1972).

The control group

Whenever possible, two control patients were studied for each relapsed or chronic sputum-positive patient. All had sputum-positive pulmonary tuberculosis with drug-susceptible organisms. Their names were identified from the Birmingham tuberculosis register, being the entries immediately before and after the entry for each relapsed or chronic positive patient. The information used in this study was obtained from the patients' case notes. Statistical significance was tested using Student's t-test or the χ-square test where appropriate.

RESULTS

There were 41 relapsed patients and 4 chronic sputum-positive patients. One of the latter also fell into the relapsed group, making a total of 44 patients. There was little difference in the numbers presenting each year (9–12). Of the 88 control patients we wished to study, 21 had died before relapse occurred in the index patient and they were therefore excluded. None of these patients had relapsed before death. One had died of pulmonary tuberculosis one month after chemotherapy was started (in 1969). Nine relapsed patients were not on the Birmingham tuberculosis register, having lived elsewhere at the time of original presentation. As two controls were selected for each relapsed or chronic positive patient, this reduced the number by eighteen. Four controls were lost to follow-up. A total of 45 control patients was therefore studied. The sex ratio, mean age and numbers of married, divorced, single or separated patients were almost identical in the two groups. There was one child in each group. There was no difference in the radiographic extent of disease but the number of control patients with cavitation (23) was higher than in the relapsed group (15). This difference is not statistically significant.

Table I shows some other factors which could be relevant. The numbers are in general too small for statistical evaluation but the results suggest that patients of Asian origin are less likely to relapse than other patients and that those who have a high alcohol intake, smoke or have had a previous gastrectomy may be more likely to relapse. No patient who relapsed was a diabetic. The duration of chemotherapy actually taken, according to the notes, is shown in Table II, for each group. Significantly more relapsed than control patients had less than 18 months chemotherapy while significantly more control patients had 18 months or more. Irregular chemotherapy was noted in 10 (53%) of the relapsed and chronic sputum-positive patients who had 18 months or more total duration of chemotherapy, but in only 2 (6%) of the control group. (Irregular chemotherapy included patients: who had taken premature discharge against medical advice; whose urine was negative for PAS; who admitted irregularity of treatment; or whose clinic attendance was unsatisfactory.) Nine patients in the relapsed and chronic sputum-positive group had apparently adequate chemotherapy. Certain risk factors were identified

Table I. Some characteristics of patients in the relapsed and chronic sputum-positive (CP) group and in the control group

	Relapsed and CP patients	*Control patients*
Asian origin	4	12
Alcohol intake excessive	11	4
Smokers	38*	26
Gastrectomy	7	3
Diabetes	0	3
Pneumoconiosis	1 (silicosis)	1 (coal)
Total	44	45

* Difference from control $0.05 > P > 0.01$ (χ^2)

Table II. Duration and regularity of chemotherapy

Chemotherapy	*Relapsed and CP patients*	*Control patients*
Inadequate duration		
None	3	1
Less than 12 months	14	5
12–17 months	8	2
Total	25*	8
Adequate duration (18 months or more)		
Regular	9	35
Irregular	10	2
Total	19*	37
Overall total	44	45

* Difference from control $P < 0.01$ (χ^2).

Table III. Possible reasons for relapse or chronic sputum-positive state in patients who had apparently adequate chemotherapy

Reason	*No. of patients*
Gastrectomy	2
Psychiatric history (depression)	2
Alcoholism	1
Technical relapse only	2
No apparent reason	2

in some of these patients and are shown in Table III. No reason for relapse was identified in four patients, of whom two were technical relapses in that only one positive sputum was obtained, no further treatment was given and there was no subsequent evidence of relapse on other grounds. Therefore, in four years only two patients without risk factors relapsed. One was subsequently treated, the other died of bronchopneumonia shortly after the positive sputum was found.

Of the 41 patients who relapsed, 21 were discovered at routine follow-up, 14 were referred again by their general practitioner and six were detected after admission to hospital with another initial diagnosis. In other words about five patients per year with risk factors were found to have relapsed at a routine follow-up visit. It is clearly important to know how long the interval was between the last positive sputum and the discovery of relapse as this will indicate whether any time limit can be set for the duration of follow-up.

In Table IV we show the numbers of patients who relapsed, subdivided according to the duration of chemotherapy and the interval before relapse. Because adequate chemotherapy was not employed before 1955, patients treated then are considered separately.

Table IV. Numbers of relapsed patients related to duration and regularity of chemotherapy and interval before relapse

Duration of chemotherapy (months)	*Chemotherapy commenced* Before 1955		1955 or later	
	No.	Interval*	No.	Interval*
0	3	26 ±1	0	—
Less than 17	6	20 ±2.2	13	7.15 ± 4.98
18 or more (regular)	0	—	9	9.83 ± 3.4†
18 or more (irregular)	0	—	10	5.88 ± 2.95†
18 or more total	0	—	19†	7.7 ± 4.95
Overall total	9	21.6 ± 3.5	32	7.5 ± 4.88

* Interval = Time (years) between last positive sputum and relapse (Mean ± S.D.)
† $P < 0.05$.

There were nine such patients and they had a mean interval of over 20 years before relapse. When the patients treated after 1955 are considered, the only difference found was that patients who had irregular chemotherapy for 18 months or more had a significantly shorter interval than those who had apparently regular chemotherapy for 18 months or more. The four patients in whom no cause for relapse was found had a mean interval of 11 years before relapse.

DISCUSSION

The need to review the practice of long-term follow-up in pulmonary tuberculosis has been previously discussed (Leading Article, *Tubercle* 1973; British Thoracic and Tuberculosis Association 1975). We consider that this study strongly supports the view that long-term follow-up in pulmonary tuberculosis should be restricted to the following categories: (1) patients who are known or suspected to have received chemotherapy of inadequate duration or to have had irregular chemotherapy and (2) patients who are considered to be at risk of relapse for the reasons discussed, namely high alcohol intake, gastrectomy and severe mental illness. The true reason for relapse in these patients may well be that they did not take their chemotherapy properly. There is no evidence in our study that diabetics require long-term follow-up; indeed a previous report from Birmingham has shown that their response to treatment is excellent (Luntz 1961). In the four years covered by this study, only two patients who had had adequate chemotherapy relapsed and required treatment. It should now be considered undesirable to follow up patients who are free from risk factors and who, on careful scrutiny, are considered to have had adequate chemotherapy. There would be considerable savings in manpower which could perhaps be used to apply even stricter supervision of chemotherapy in certain patients. The duration of follow-up in patients who do require it must be indefinite because of the long intervals before relapse shown by those who were treated before 1955. It may, of course, be difficult to do this in uncooperative patients. It is difficult to know how long to follow-up adequately treated patients without risk factors after completion of chemotherapy, if they should be followed up at all. Pearce and Horne (1974) showed that 76% of all patients who relapsed did so within 5 years of initiation of treatment and using evidence such as this it has recently been our policy to follow up adequately treated patients for five years only. When our results are considered, however, it seems unlikely that many relapses would be discovered in this way. A further study is needed to clarify this point.

ACKNOWLEDGEMENTS

We are indebted to Dr F. A. J. Bridgwater, Public Health Laboratory Service, Birmingham, for his help in identifying the patients studied; to the staff of Birmingham Chest Clinic for clerical help; to Dr H. E. Thomas for the information on patients with drug-resistant organisms; and to Mrs Pamela Jackson for her secretarial assistance.

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A COMPARISON OF SALBUTAMOL GIVEN BY PRESSURE-PACKED AEROSOL OR NEBULIZATION VIA IPPB IN ACUTE ASTHMA

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Summary

Salbutamol was given by pressure-packed aerosol or nebulizer via IPPB to patients with acute asthma to compare the effectiveness of these methods of inhalation.

The results show that both methods produce significant bronchodilatation even in patients admitted with moderately severe asthma (FEV_1 about 38% predicted) but a slightly greater improvement may be achieved by IPPB nebulization.

Our findings indicate that supervised inhalation of a pressure-packed aerosol of salbutamol may be useful for the initial treatment of asthmatic attacks but confirm the marginal advantage of IPPB nebulization, which should be reserved for patients unable to inhale from a pressure-packed aerosol or failing to respond to its treatment.

Introduction

The best method of administering sympathomimetic bronchodilator drugs to patients suffering from acute asthma remains debatable (Williams & Seaton 1977). The inhaled route is commonly used and some clinicians nebulize a solution of bronchodilator using an intermittent positive-pressure breathing (IPPB) device in preference to other methods of aerosol administration (Choo-Kang & Grant 1975). There is, however, evidence that delivery by pressure-packed aerosol may be as effective in terms of spirometric improvement as nebulization with IPPB (Cohen & Hale 1965), which might avoid dependence on expensive equipment and highly trained staff and enable treatment to begin at home and on admission to hospital. As this is of practical importance we have compared the effects of salbutamol given by pressure-packed aerosol and by nebulization via IPPB in patients admitted to hospital with acute asthma to assess respective benefit.

Patients and Methods

Patients were studied within 12 hours of admission to hospital with acute asthma. Recruitment of patients was limited to those who could perform a forced expiratory manoeuvre and were not too ill to cooperate. Treatment with intravenous aminophylline, hydrocortisone and oral prednisolone was continued as prescribed throughout the study but no patient received salbutamol for at least 4 hours before the trial.

400 μg of salbutamol (four puffs) from a pressure-packed aerosol was compared with 5 mg salbutamol (1 ml of 0.5% solution of salbutamol made up to a total of 3 ml in the micro-nebulizer with normal saline) by IPPB from a Bird nebulizer given over 10 min.

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Ten patients were studied; five received 400 μg of salbutamol from a pressure-packed aerosol followed by 5 mg of salbutamol by IPPB and 5 patients received the treatment in the reverse order. There was random allocation to each treatment group. The forced expiratory volume (FEV$_1$) and forced vital capacity (FVC) were measured (Vitalograph) at the beginning of each study. After the first treatment measurements of FEV$_1$ and FVC were repeated after 10 min and the second treatment was then given. Ten minutes later the measurements were repeated again.

All measurements were calculated as a percentage of predicted normal values and when grouped are recorded as mean ±1 SD. The paired *t*-test was used to assess significance (significance being $P = 0.05$ or less).

RESULTS

Five patients (four females and one male, mean age 43 years) with an FEV$_1$ of 37% (±13%) of predicted normal (mean 0.9 litres) received the pressure-packed aerosol first (Group A) and five patients (four females and one male, mean age 45 years) with an FEV$_1$ of 38% (±9%) of predicted normal (mean 1.1 litres) received nebulized salbutamol via IPPB first (Group B).

In Group A there was a significant increase in FEV$_1$ and FVC after treatment with salbutamol from the pressure-packed aerosol with a further significant improvement after the second treatment with nebulized salbutamol (Fig. 1).

In Group B significant increases in FEV$_1$ and FVC followed treatment with nebulized salbutamol but no additional improvement was found following the second treatment with a pressure-packed aerosol (Fig. 2).

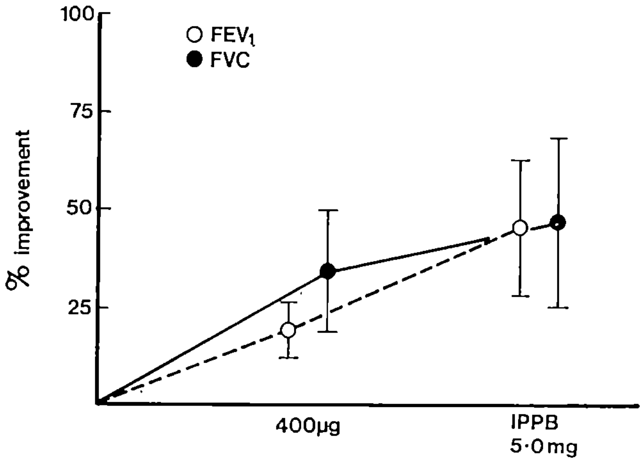

Fig. 1. The percentage improvement in percentage predicted values for FEV$_1$ and FVC after being given 400 μg of salbutamol from pressure-packed aerosol followed by 5 mg of salbutamol by IPPB (Group A patients)

DISCUSSION

Preliminary studies had showed that 400 μg of salbutamol from a pressure-packed aerosol produced a maximum improvement in both FEV$_1$ and FVC in patients with acute asthma but not in those with mild asthma (Alliott et al. 1972) and, therefore, this dosage was chosen for comparison with 5 mg inhalation of salbutamol by IPPB, which has been shown to be as effective as inhalation of 10 mg (Choo-Kang et al. 1970).

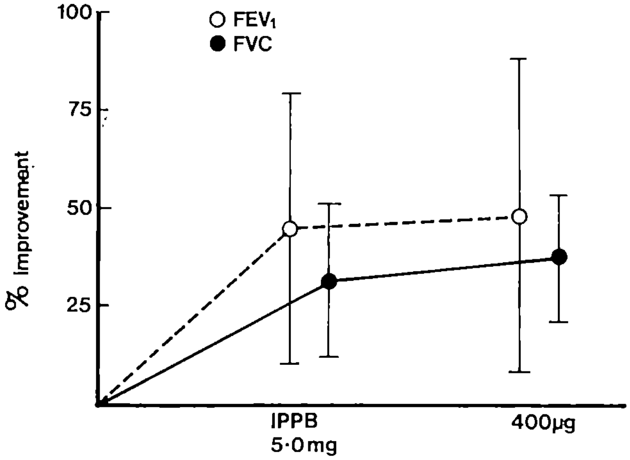

Fig. 2. The percentage improvement in percentage predicted values for FEV_1 and FVC after being given 5 mg of salbutamol by IPPB followed by 400 μg of salbutamol from a pressure-packed aerosol (Group B patients)

Our results show that significant improvement in ventilatory capacity followed supervised salbutamol administration given either from a pressure-packed aerosol or by IPPB with nebulization but that the nebulized dose produced a greater increase especially in FEV_1. These results agree with findings of Choo-Kang and Grant (1975), who used 10 mg of salbutamol by IPPB but in patients who were not acutely ill. Inspection of our results, however, also demonstrates that although IPPB may achieve significantly greater bronchodilatation the extra increase in ventilatory capacity is slight compared with the overall bronchodilator effect produced by each method of inhalation. The benefit from IPPB is, therefore, marginal in terms of bronchodilatation, although IPPB may have other advantages which may be additive.

We therefore suggest that our results show that 400 μg of salbutamol administered under supervision from a pressure-packed aerosol provides significant spirometric improvement in patients with acute asthma, which is almost as good as produced by nebulization. In practice clinicians can thus first employ a pressure-packed aerosol and only consider other methods of inhalation if this is unsuccessful.

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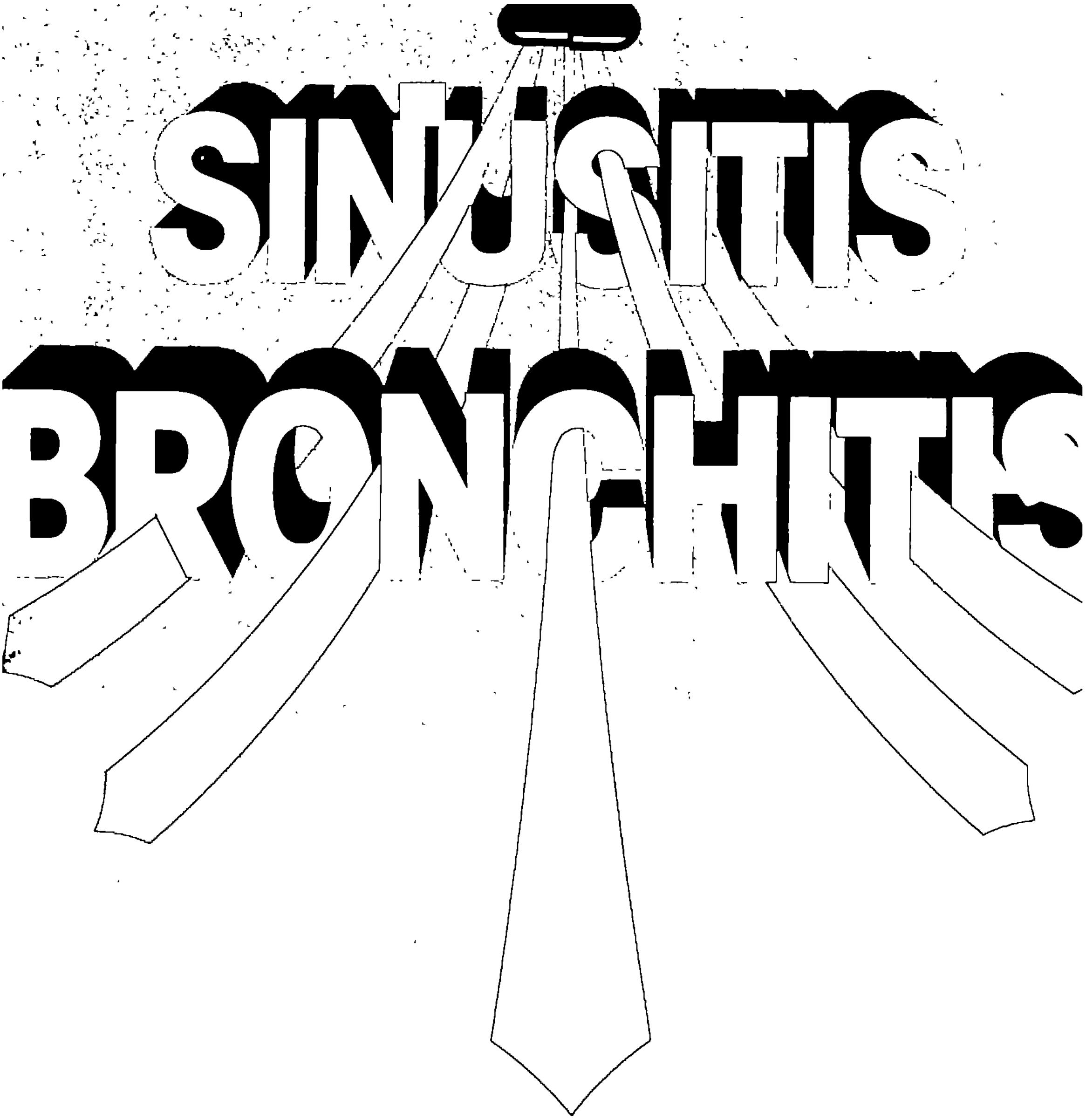

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1. *Chemother.*, 1975, Vol 21 (Suppl. 1), 1-7
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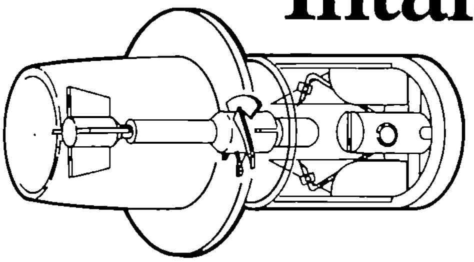

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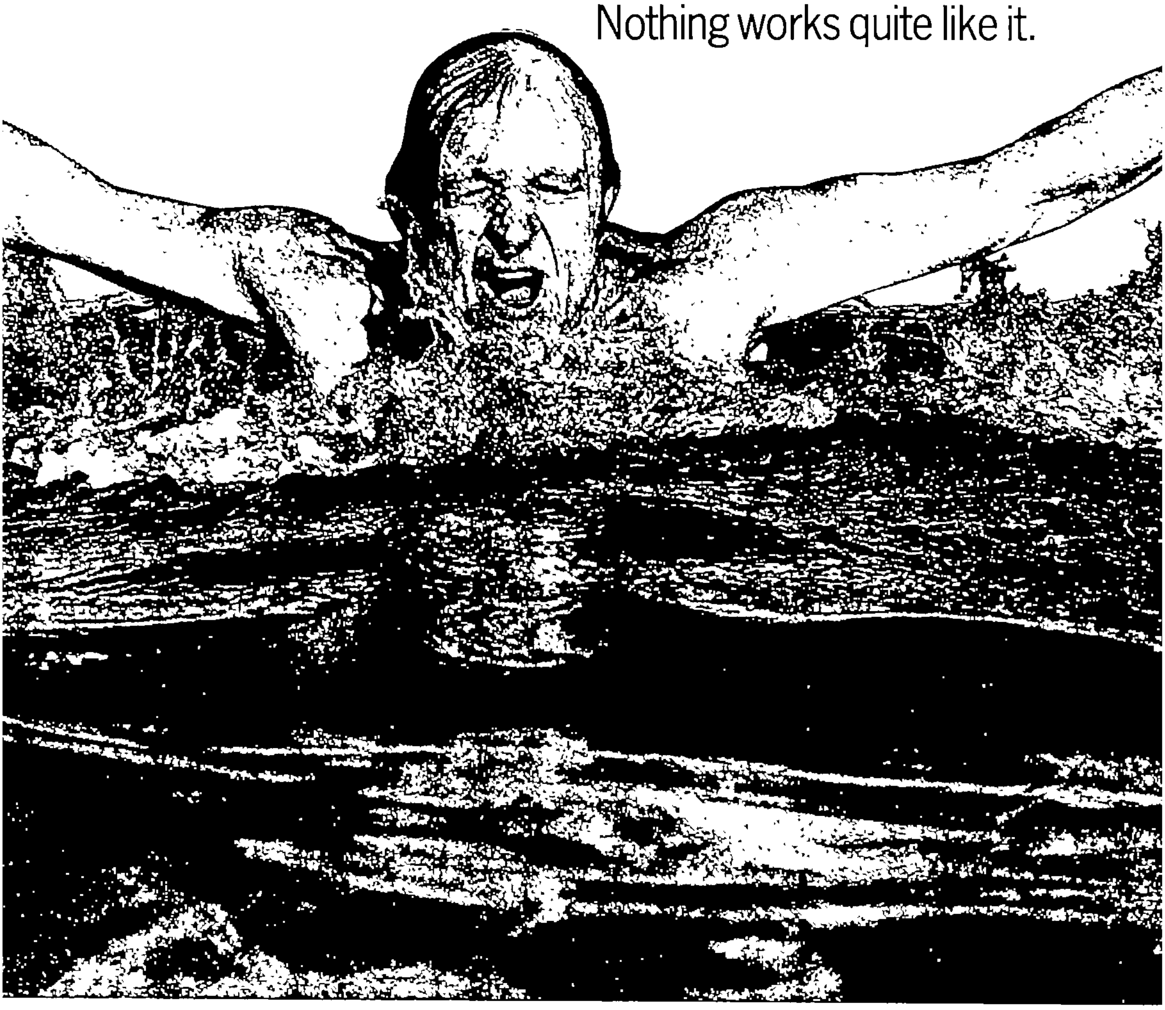

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Br. J. Dis. Chest (1978) 72, 225

BRL10833 IN INHIBITING EXERCISE-INDUCED BRONCHOCONSTRICTION IN ASTHMATIC CHILDREN

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Summary

A double-blind controlled exercise challenge study has been performed in 16 asthmatic children to show the effectiveness of BRL10833 in inhibiting exercise-induced bronchoconstriction. The children attended the respiratory laboratory on four occasions within the space of two weeks; on each occasion a routine 6-min exercise test was performed. At the first visit no drugs were given before the exercise test and all the children demonstrated abnormal exercise-induced bronchoconstriction as measured by peak expiratory flow rate (PEFR), forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC). On the other three occasions the children were given sodium cromoglycate, BRL10833 or placebo medications before the exercise test. After sodium cromoglycate administration four children showed complete blocking and four showed partial blocking of exercise-induced bronchoconstriction. After BRL10833 four children showed complete blocking and six showed partial blocking of exercise induced bronchoconstriction. Placebo administration produced complete blocking of exercise-induced bronchoconstriction in three and partial blocking in two children. The results indicated that BRL10833 was almost as effective as sodium cromoglycate in inhibiting exercise-induced bronchoconstriction and placebo, although less effective than the two preparations, did afford protection from exercise-induced bronchoconstriction in some of the children.

INTRODUCTION

As well as showing clinical benefit in childhood asthma sodium cromoglycate blocks exercise-induced bronchoconstriction both in adults (Davies 1968) and children (Blackhall & Jones 1970; Godfrey 1974; Lenney & Milner 1978).

A new compound, BRL10833 (Beecham Research Laboratories) is in tablet form, but with pharmacological and toxicological properties similar to those of sodium cromoglycate powder (Spicer et al. 1975). The present study was undertaken to determine whether BRL10833 tablets could inhibit exercise-induced bronchoconstriction and to compare this effect with that of sodium cromoglycate powder.

Patients and Methods

Methods

Ventilatory function was assessed by the Wright peak flow meter and a wet spirometer (Morgan M_2) from which forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1)

measurements were obtained. Each child came to the laboratory on four occasions on separate days within the space of two weeks. Wherever possible all four visits occurred at the same time of day. On arrival in the laboratory peak expiratory flow rate (PEFR) was determined and the best of three consecutive flows was recorded. FVC and FEV_1 was measured, the best of two being recorded. All measurements were repeated 25 min later and again 2, 5, 10, 20 and 25 min after running along an indoor corridor for 6 min. On all occasions the children's heart rate exceeded 160 beats/min at the end of the run. On the three subsequent visits an identical procedure occurred except that 20 min before the run each child received one of the following combinations of therapy:

1. Sodium cromoglycate 20 mg by spinhaler+placebo tablet
2. Placebo powder by spinhaler+100 mg BRL10833 tablet
3. Placebo powder by spinhaler+placebo tablet

The medications were previously coded at Beecham Research Laboratories and as the code was not broken until the end of the study the medications were given under double-blind conditions.

Patients

Seventeen children (11 boys and 6 girls) took part, their ages ranged from 7 to 13 years (mean 10 years). All were attending paediatric out-patient clinics in Nottingham with a diagnosis of childhood asthma. Ten of the children had a history of eczema and 14 had a family history of asthma. Serum IgE levels were not measured in any patient nor were skin tests performed. Two children were receiving regular bronchodilator therapy only. Eight were receiving bronchodilators and sodium cromoglycate. Five were receiving regular beclomethasone by inhalation and two were receiving oral prednisolone (5 mg on alternate days). Except for the two children taking oral prednisolone all therapy was stopped for at least 12 hours before exercise testing. On arrival in the laboratory all children were clinically well, 15 had no wheeze on chest auscultation and two had minimal expiratory wheeze.

RESULTS

One patient was not included in the analysis of results as he was not able to complete the full 6 min run according to the protocol. The results of the remaining 16 patients

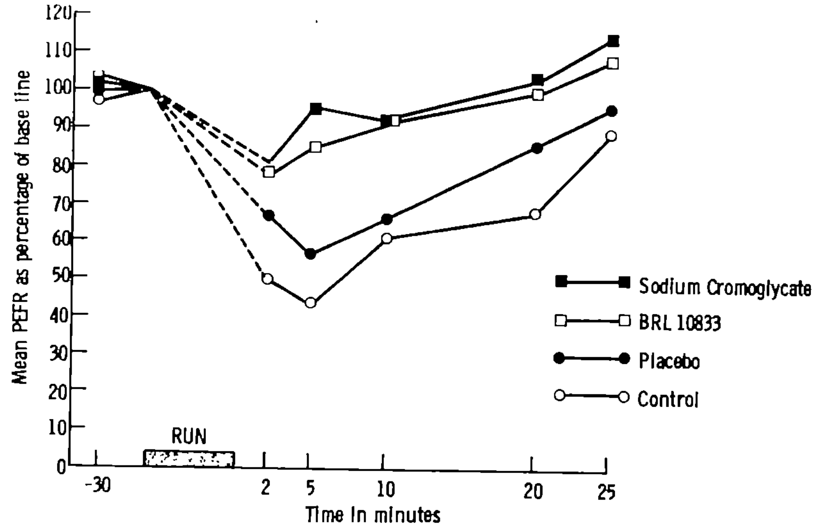

Fig. 1. Mean peak expiratory flow rate (PEFR) before and after four 6-min runs in 16 asthmatic children. The results are expressed as a percentage of the readings obtained immediately prior to the run

have been expressed as a percentage of the reading immediately before the run. The mean maximal percentage fall in PEFR was 55% after the initial control run, 42% after the placebo run, 20% after the BRL10833 run and 20% after the sodium cromoglycate run (Fig. 1). The mean maximal percentage fall in FEV₁ was 45% after the initial control

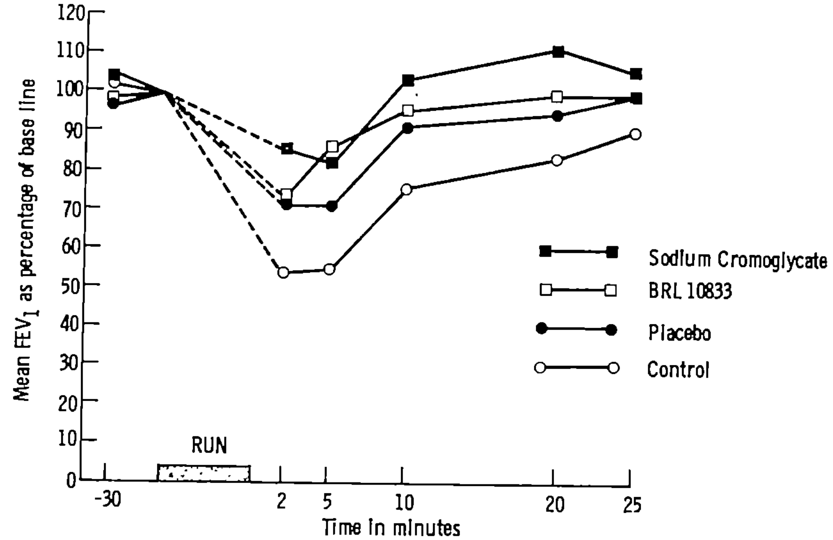

Fig. 2. Mean forced expiratory volume in 1 sec (FEV_1) before and after four 6-min runs in 16 asthmatic children. The results are expressed as a percentage of the readings obtained immediately prior to the run

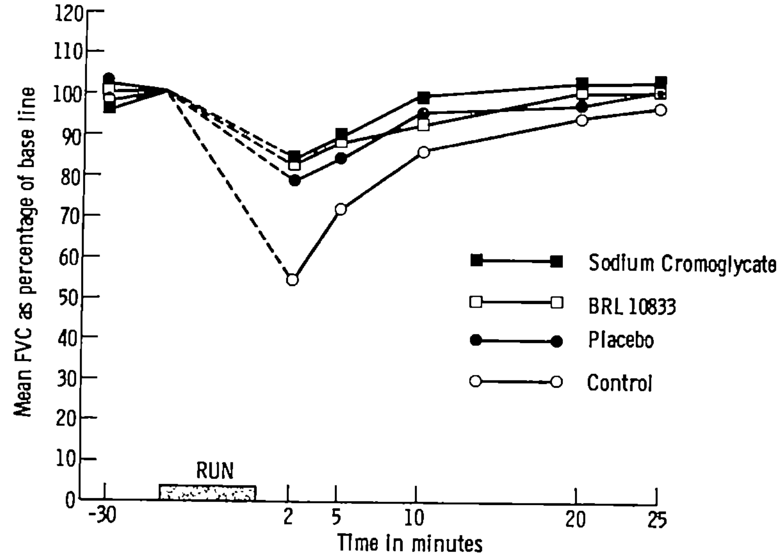

Fig. 3. Mean forced vital capacity (FVC) before and after four 6-min runs in 16 asthmatic children. The results are expressed as a percentage of the readings obtained immediately prior to the run

run, 28% after both placebo and BRL10833 runs and 15% after the sodium cromoglycate run (Fig. 2). The mean maximal percentage fall in FVC was 45% after the initial control run, 20% after the placebo run, 18% after the BRL10833 run and 17% after the sodium cromoglycate run (Fig. 3). The PEFR, FEV_1 and FVC results have also been examined in terms of net areas after exercise, the reading immediately before the exercise again being taken as the baseline. For all three parameters these baseline measurements varied on the four test occasions but on statistical grouping they were confirmed not to be significantly different for the four groups.

A Friedman two-way analysis of variance was used to test for differences between the four schedules and if a significant difference occurred, a multiple comparison procedure was used to show where these differences occurred. In no case was there a significant difference between placebo, sodium cromoglycate or BRL10833. The greatest degree of post-exercise bronchoconstriction occurred with no drug, whatever parameter was measured and all significant differences which occurred were between the three test drugs and no drug. A summary of these significant differences is shown in Table I. It can be seen that sodium cromoglycate comes out most favourably, with BRL10833 next. With PEFR areas and FEV_1 maximal percentage fall, placebo was not significantly different from no drug and on all other comparisons was significant only at the 5% level.

Table I. Summary of significant differences between the three test drugs and control

	Placebo	*Sodium cromoglycate*	*BRL10833*
Peak flow			
Areas	NS	$P<0.001$	$P<0.01$
Maximum fall (%)	$P<0.05$	$P<0.001$	$P<0.001$
FEV_1			
Areas	$P<0.05$	$P<0.001$	$P<0.05$
Maximum fall (%)	NS	$P<0.001$	$P<0.01$
VC			
Areas	$P<0.05$	$P<0.001$	$P<0.01$
Maximum fall (%)	$P<0.05$	$P<0.001$	$P<0.01$

Table II. No. of children with complete, partial or no effective blocking of exercise-induced bronchoconstriction after the initial control run and after administration of placebo, BRL10833 and sodium cromoglycate

Therapy given prior to each run	*Complete blocking**	*Partial blocking†*	*No effective blocking‡*
Initial control run: no therapy	0	0	16
Placebo	3	2	11
BRL10833	4	6	6
Sodium cromoglycate	4	4	8

*Maximum post-exercise fall in PEFR <10%.
†Maximum post-exercise fall in PEFR 10–25%.
‡Maximum post-exercise fall in PEFR >25%.

After the initial control run the maximum percentage fall in PEFR was greater than 25% in all 16 children. After the placebo run three of the children effectively had complete blocking of exercise-induced bronchoconstriction compared with four after the BRL10833 run and four after the sodium cromoglycate run. Two of the 16 children had considerable reduction in exercise-induced bronchoconstriction after the placebo run compared with six after the BRL10833 run and four after the sodium cromoglycate run (Table II).

Discussion

Although sodium cromoglycate has been used in the treatment of asthma for 10 years the reasons for its effectiveness are not fully known. It is therefore difficult to assess the reliability of screening procedures designed to detect other compounds which may give similar protection to asthmatics. In animal studies sodium cromoglycate has been shown to be most reliably active in passive cutaneous anaphylaxis (PCA) and passive peritoneal anaphylaxis (PPA) test systems in the rat (Cairns et al. 1972). BRL10833 is a nitroindanedione chemically unrelated to sodium cromoglycate but in animal studies (PCA and PPA tests) it produces cross-reacting tachyphylaxis with sodium cromoglycate, indicating that both drugs probably have the same mode of action (Spicer et al. 1975).

In the present exercise challenge study BRL10833 results compare favourably with those of sodium cromoglycate in inhibiting exercise-induced bronchoconstriction. Because of the high placebo response we were unable to show statistically significant results after the BRL10833 run compared with those after the placebo run. For the same reason, however, we were also unable to show statistically significant results after the sodium cromoglycate run compared with those after the placebo run. The placebo response to exercise testing has been well documented previously (Silverman 1972; Lenney & Milner 1978) and significant reduction in exercise-induced bronchoconstriction has been found in 41% of cases (Godfrey & Silverman 1973). Our exercise tests were unsophisticated and relatively non-standardized, in that no effort was made to determine the amount of work done. A previous paper has shown, however, that free run exercise produces consistentely more exercise-induced bronchoconstriction than either treadmill or ergometer exercise (Anderson et al. 1971) and as all our patients ran for 6 min along an indoor corridor and all had pulse rates greater than 160/min afterwards, we considered they had undergone a prolonged severe exercise.

BRL10833 is rapidly absorbed in fasting individuals, peak serum levels being achieved in 60 min after oral administration in man. If BRL10833 is taken after food the absorption rate is significantly reduced for the first 1 or 2 hours. There is some evidence to suggest absorption is faster in children and a previous study (Pauwels et al. 1976) suggested 15 min was the optimum time between oral administration and antigen challenge for best protection against antigen-induced bronchoconstriction. In this study we allowed 20 min between oral administration and exercise challenge. Most but not all children had not eaten for 2 hours before arrival at the laboratory and it may be that the results after BRL10833 would have been improved had we allowed longer than 20 min for absorption or insisted on complete fasting for 4 hours before testing. All children tolerated the BRL10833 tablets well and no side effects were noted.

The relationship between exercise-induced bronchoconstriction and clinical asthma is at present unclear. Some children show protection from exercise-induced bronchoconstriction by a drug in the laboratory but are not helped clinically by the same drug. Exercise tests therefore have limitations and conclusions must be stated with caution. We feel however that a number of points emerge from the present study:

1. BRL10833 is an active drug which is effective in inhibiting exercise-induced bronchoconstriction in some asthmatic children.
2. BRL10833 seemed almost as effective as sodium cromoglycate in inhibiting exercise-induced bronchoconstriction.
3. Because of the high placebo response any study assessing the efficacy of drugs in inhibiting exercise-induced bronchoconstriction must be carried out under double-blind controlled conditions.
4. Since the completion of this study this compound has been withdrawn, but this study indicates that this group of compounds deserves further development.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Chest and Heart Foundation and from Beecham Pharmaceutical Company.

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SULFAMETOPYRAZINE PROPHYLAXIS IN CHRONIC BRONCHITIS

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Summary

From a double-blind randomized controlled trial by 32 general practitioners on 218 patients with chronic bronchitis it appeared that sulfametopyrazine given once a week over one winter reduced the number of respiratory illnesses and the loss of time from work to about half that of a control group. It had no effect on time off work in individual spells of illness nor on the amount and purulence of sputum. Side-effects were few and mild.

Introduction

Patients with chronic bronchitis have more acute respiratory illnesses than others, especially in winter. Many trials have been done to see if long-term prophylactic chemotherapy reduces their number and severity. A BTA report (Francis & Spicer 1960) suggested that penicillin and tetracycline might not cut the number of attacks but they were shorter and caused less time off work. The Medical Research Council study (1966) using tetracycline came to the same conclusion. Some studies (Johnston et al. 1969) appeared to show fewer attacks, but the benefit was confined to patients with frequent exacerbations. Sulphonamides were less effective than other drugs (Francis et al. 1961) but a long-acting one, sulphormethoxine, given once a week reduced attacks to half (Pines 1967).

Sulfametopyrazine is a long-acting sulphonamide with a half life in blood of 65 hours. A dose of 2 g once a week produces peak blood levels of about 100 μg/ml which fall to about 30 μg/ml after a week. In one study 20 patients treated for a year had fewer exacerbations than 18 control subjects but the difference was not statistically significant (Darke et al. 1972). A larger double-blind trial was therefore undertaken.

Patients and Methods

General practitioners in Sheffield and Nottinghamshire were asked to submit to the trial patients aged 30–65 years with winter cough and phlegm for 3 years or more and an exacerbation leading to loss of work or activity in the previous winter. The ideal patient was at least able to do light work and, for a woman, to look after the house. Excluded were those too disabled to leave the house and garden and those on corticosteroids, in heart failure or with bronchiectasis.

Patients were allocated at random to receive either 2 g of sulfametopyrazine or an identical placebo tablet, once a week from the beginning of November 1975 to mid-March 1976 (20 weeks). No steps were taken to make the sputum non-purulent at the start. The doctors were free to treat exacerbations as they saw fit but the patients were instructed to keep taking the trial tablets.

Before the start the number of bronchitic exacerbations in the previous winter, the smoking habits and the peak expiratory flow rate were recorded. Patients were then seen monthly and fresh respiratory illnesses and resulting time off work were recorded. The patients made their own estimate of the amount of sputum they were producing and brought an early morning sample for the doctor to grade its purulence. A month after the end of the trial their smoking habits and peak expiratory flow rate were recorded again. Patient and doctor gave an estimate of the severity of the bronchitis during the trial compared with previous winters and gave reasons for their opinions.

RESULTS

Two hundred and fifty-four patients were entered. Twelve were withdrawn because of side effects and one because he felt too well to take tablets. One died from a heart attack and another from a stroke. The records of some were incomplete. Those where the peak expiratory flow rate had been recorded at the beginning and at the end were best documented and the rest were discarded. This left 218 for analysis. Table I shows the groups to be well matched. More patients in the treated group had a peak expiratory flow rate below 150 litres/minute but the difference was not significant.

Fresh respiratory illnesses in the treated group were 58% of those occurring among the controls (Table II). The findings were similar in those at work during the trial (96 treatment, 102 control; housewives were regarded as working). Most illnesses led to time

Table I. Comparison of treated and control groups

	Treatment	*Control*
Number	110	108
In regular work	96	102
Mean age (years)	55	55
Men (%)	79	71
Cigarette smokers (%)	59	58
Mean number of respiratory illnesses previous winter	2.2	2.3
PEFR (litres/minute)	239	260
Given influenza vaccine (%)	30	31

Table II. Number of respiratory illnesses and score for change in severity of bronchitis (mean ± SD)

	Treatment	*Control*	*t*	*P*
Number of illnesses per patient (all patients)	0.83 ± 0.97	1.43 ± 1.36	3.74	<0.001
Number of illnesses per patient (workers)	0.78 ± 0.92	1.42 ± 1.36	3.90	<0.001
Number of illnesses causing time off work	0.62 ± 0.90	1.29 ± 1.42	3.99	<0.001
Change in severity of bronchitis				
Patient	1.01 ± 0.92	0.62 ± 1.05	2.90	<0.005
Doctor	0.90 ± 0.82	0.49 ± 0.85	3.61	<0.001

off work and this happened twice as often in the placebo group. These differences are statistically highly significant. There was no difference in the mean number of days off work per illness (11 treatment, 10.5 control).

At the end of the trial patients and doctors stated whether, compared with previous winters, the bronchitis had been much better (+2), better (+1), the same (0), worse (−1) or much worse (−2). This scoring system showed a statistically highly significant difference favouring treatment (Table II). Patients and doctors gave reasons for their opinions. In the treatment group there were 62 favourable and 7 adverse comments compared with 26 favourable and 18 unfavourable in the control ($\chi^2 = 12.75$, 1 degree of freedom, Yate's correction, $P < 0.001$).

A score was allotted to the amount and purulence of sputum throughout the trial. There was no significant difference between the groups.

At the end of the trial, neither group showed a significant change in peak expiratory flow rate from the initial levels.

Six patients in the treated group and 24 in the control group stopped smoking during the trial.

Side effects

There were seven withdrawals in the treatment group. Four had gastric symptoms, one facial oedema, one a rash and the other had non-specific symptoms. The five withdrawn in the placebo group had mixed complaints.

Discussion

Why patients with chronic bronchitis suffer recurrent respiratory illnesses is unknown. They often harbour *Haemophilus influenzae* and pneumococci in their sputum even when it is mucoid (Miller & Jones 1964). Since the organisms are so often found without attacks, other factors must play a part in initiating them. How often this is an increase in the bacterial population or a virus or mycoplasma infection is not known. Virus infections cause a considerable proportion of respiratory illnesses in normal people and it is therefore unlikely that antibacterial agents could influence such attacks occurring in chronic bronchitics. Bronchitics have about twice as many respiratory infections as normal people (Stenhouse 1968). The number of exacerbations of illness in the sulphonamide group in this trial was 58% of the number in the control group. From this it might be suggested that the episodes had been reduced to somewhere near the levels found in normal people.

It is not surprising that time off work in individual illnesses was the same in both groups. Social factors such as the day of the week when improvement occurred affect return to work.

In the treatment group there were many favourable comments indicating less cough and breathlessness, less difficulty in clearing the chest and greater general well-being during the period of the trial. Since the comparison was double-blind it is possible that the treatment had some effect between exacerbations. One wonders whether so few treated patients gave up smoking (6 *v.* 24) because they seemed to be improving.

The number of illnesses was less than in the previous winters in both groups. A number of reasons is suggested. The earlier number was recorded from memory and a contribution from records. Patients were eligible only if they had at least one exacerbation in the previous winter, and bronchitics may go through some winters without attacks. The winter was mild. It remains that the reduction in the treatment group was to 38% and in the controls to 62% of the number of illnesses in the previous winter, a statistically highly significant difference.

Side effects were few and mild. If chemoprophylaxis is to be used in chronic bronchitis, sulfametopyrazine is a suitable drug and once weekly dosage encourages its acceptance by the patient.

ACKNOWLEDGEMENTS

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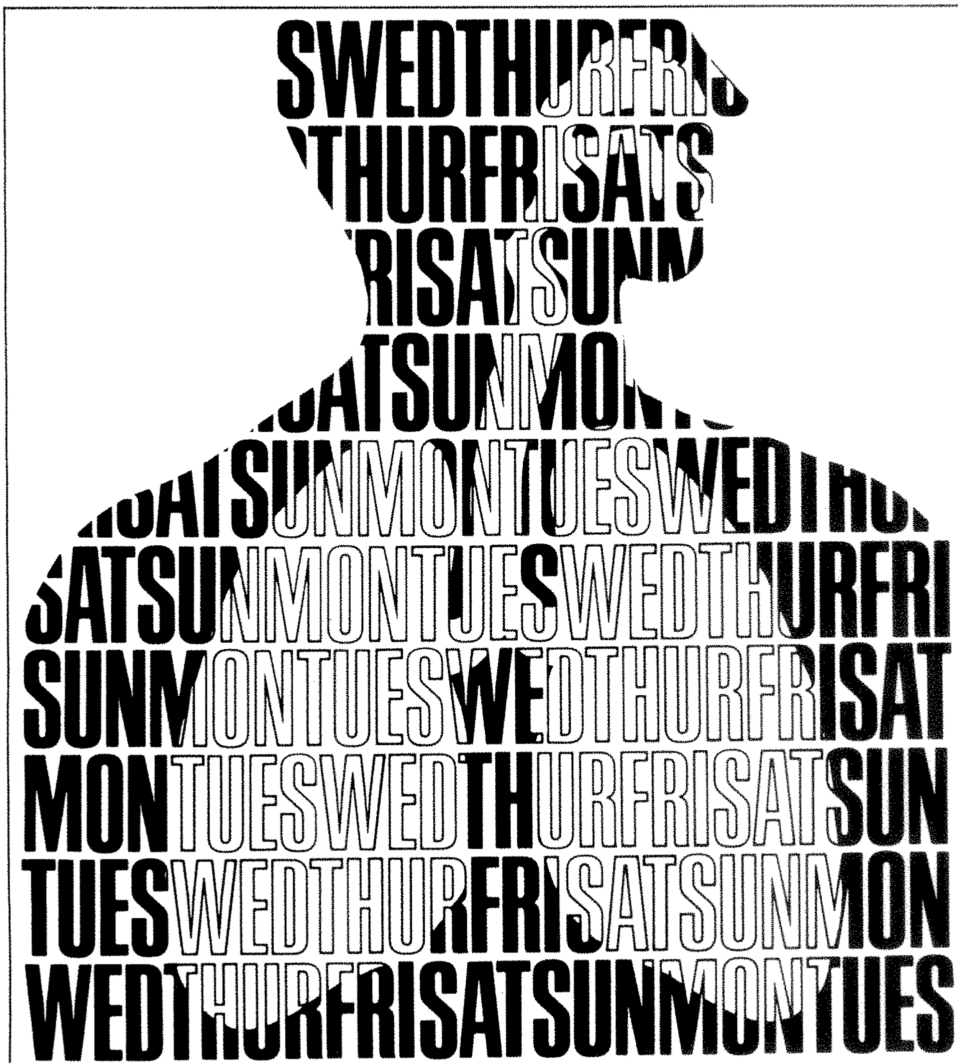

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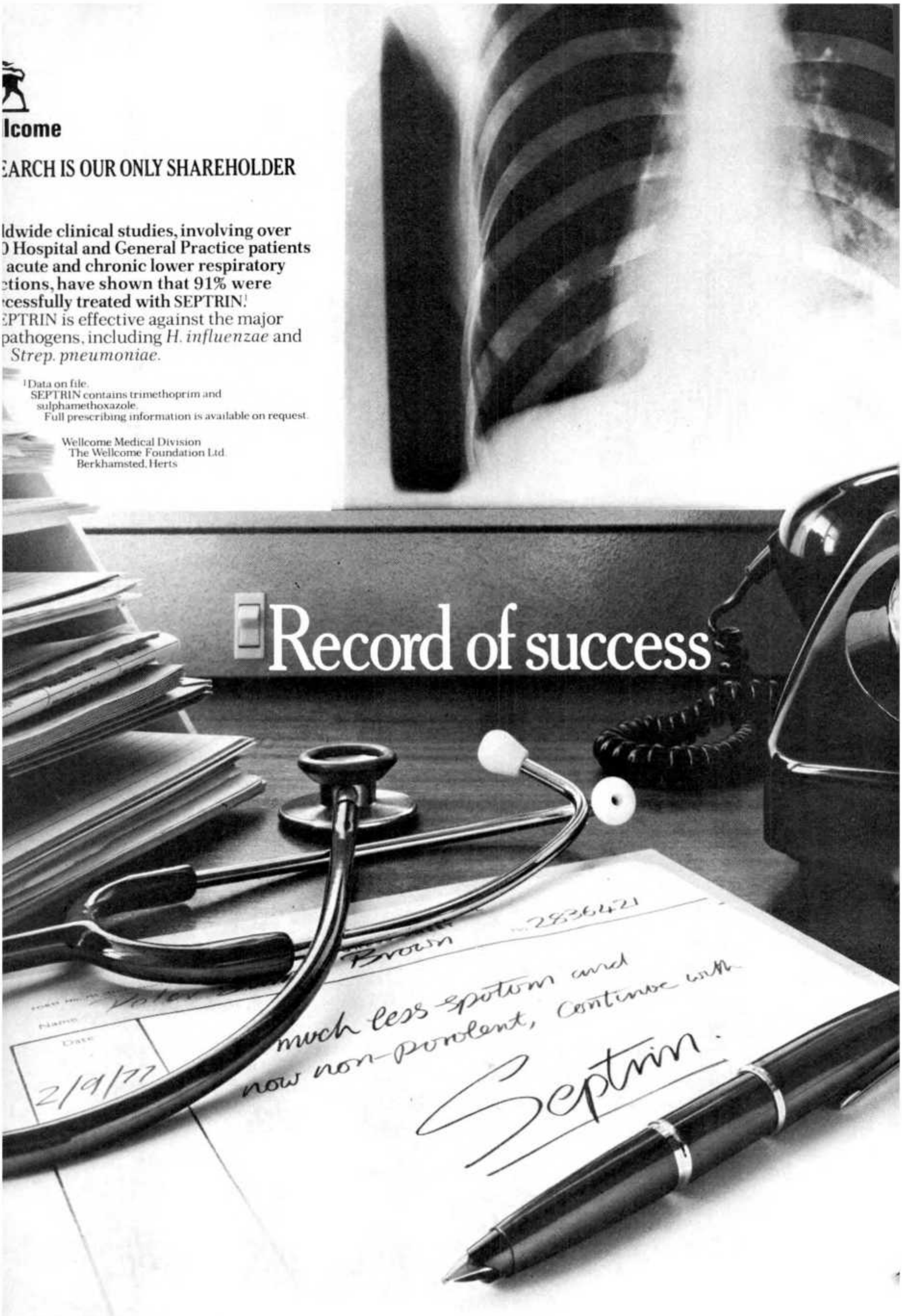

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ASPIRATION NEEDLE BIOPSY FOR SOLITARY, PERIPHERAL LUNG LESIONS: A REVIEW OF 50 EXAMINATIONS

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Summary

Percutaneous aspiration needle biopsy forms a simple method of obtaining histological material from solitary peripheral lung lesions. A new method for separating and preparing the material for histological examination is described. The results in 50 cases are recorded with a positive diagnosis in 46. The number of symptomatic complications with this technique is low. The clinical place of the biopsy in management is discussed.

Introduction

Percutaneous aspiration biopsy is a useful and simple method for obtaining histological material from solitary peripheral pulmonary lesions. This paper gives details of the histological processing method which allows concentration of the small fragmented specimen, which are often obtained by this technique, into a larger mass which can then be processed by routine methods, without risking loss of the minute fragments. Fifty such examinations are reviewed.

Materials and Methods

Material

During the period June 1974 to July 1976 aspiration needle biopsy has been carried out in 50 patients (45 males and 5 females) ranging from 46 to 80 years of age. All these patients had a solitary peripheral opacity which was demonstrated on postero-anterior and lateral radiographs, with further studies by tomography.

The procedure was not performed if the respiratory function was very poor, if the lesion was in the one remaining lung, if there was a history of bleeding diatheses of pulmonary hypertension, or if the radiological appearances suggested that it could possibly be an arteriovenous malformation.

The lesion varied in size from 1.5 cm to 6 cm as measured on the tomogram. In all these cases the radiological appearances suggested that the lesion was neoplastic.

Biopsy technique

The radiological equipment available in the radiography department of the average district general hospital is adequate for the procedure. Briefly, the technique consists in aspirating bits of material from the suspected lesion under fluoroscopic guidance for histological examination. We have found the Oslo tap needle, which is 7 cm long and fitted with a tap mount, very suitable; for deeper lesions we use an aspiration needle 10 cm long with a bore of 14g also fitted with a tap (Grech & Clark 1978). These needles reached all the peripheral lesions included in this series.

Obviously for deeper areas one would need a long aspiration needle. We prefer to position the patient so that the needle is inserted into the lesion by the shortest distance from the chest wall. The only exception to this rule is when such a lesion is in front of the scapula, in which case the approach will have to be anterior or oblique.

No mortality was recorded. The only complications encountered were slight haemoptysis in three cases and pneumothorax in ten. Only three of the pneumothorax episodes caused symptoms requiring treatment, the remainder were picked up only on the routine post-biopsy radiograph.

Agar gel method for biopsy fragments

The apparatus consisted of a Millipore micro-analysis filter unit with stainless steel support, Millipore Duralon membrane 14 μm porosity; this unit was fitted into a side-arm flash and in turn connected to a simple Venturi vacuum pump (Fig. 1). A water bath was required to maintain the agar in a molten state at 60°C. Standard apparatus was used for the processing to paraffin wax, followed by embedding using a Tissue Tek II centre.

Fig. 2 shows the apparatus set up for the treatment of three specimens, the vacuum being controlled by three-way taps and the specimens located with labelled cassettes to avoid the possibility of confusion.

The specimens arrived in the laboratory in 10% formal saline fixative and the particles were concentrated on the surface of a Duralon 14 μm membrane, included in an agar gel block and processed by standard paraffin wax technique.

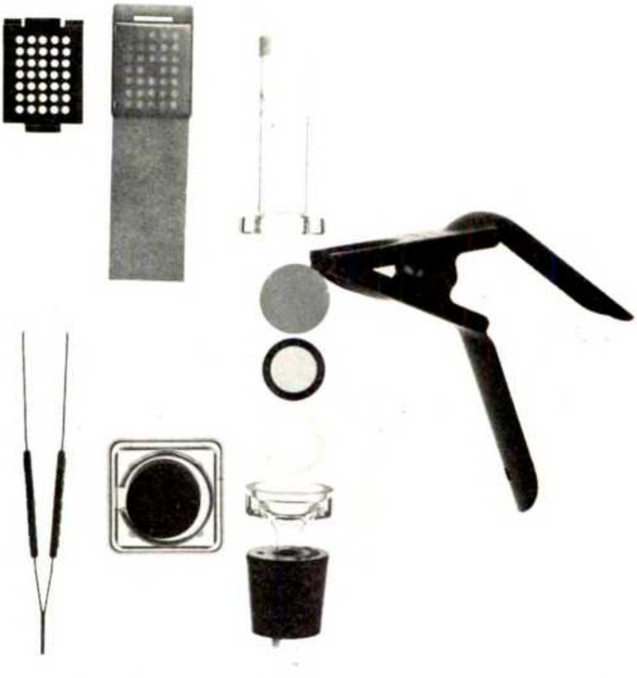

Fig. 1. Exploded view of the filtration unit showing the filter assembly and clamp. Tissue Tek cassette with filter paper (top left) and the special forceps for handling the millipore filters (both bottom left)

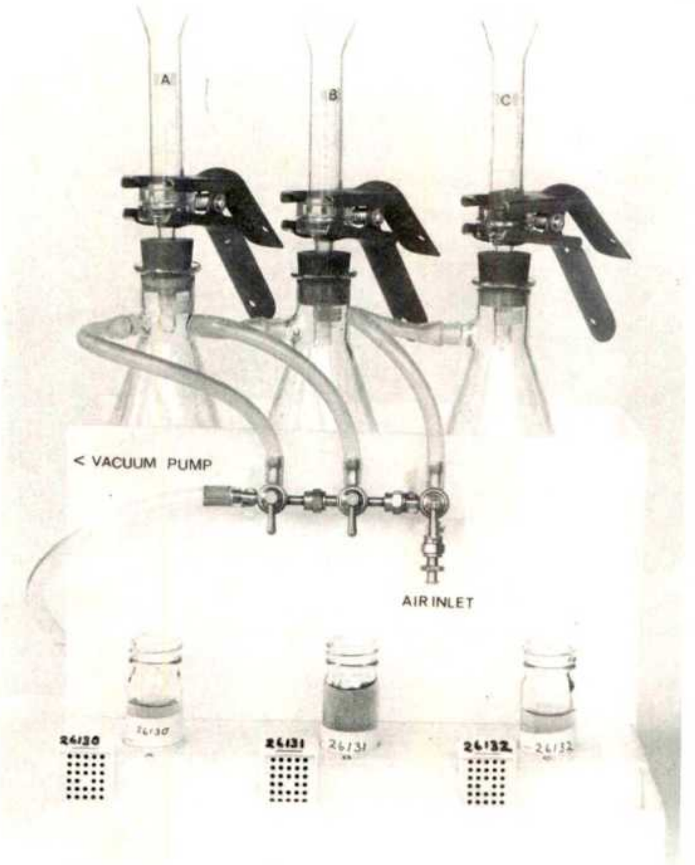

Fig. 2. A simple 'mass processing' unit

After assembling the filter unit with a wet Duralon membrane, each specimen was gently swirled to suspend the particles, and then filtered through a membrane, using minimum vacuum; the container was rinsed to ensure complete transference. The particles were deposited on the membrane and when all fluid had been drawn through, gently covered to approximately 2 cm with 2% aqueous agar at 60°C avoiding disturbing the deposit. A brief period of vacuum was allowed to anchor the membrane, and to ensure proper embedding of the fragments.

The agar was then allowed to cool, aided if required by the use of Arctic Spray. When solid the filter unit was dismantled and the agar plug and membrane extruded for 3–4 mm by pushing with a suitable rod. The ground glass face of the funnel was used as a guide to slice off the protruding plug.

The specimen consisting of the filter membrane and biopsy tissue in agar was transferred membrane down into a Tissue Tek cassette, containing a strip of moist filter paper which, when folded, wrapped the specimen (Fig. 3). The cassette cover was fitted and processing was then by standard paraffin wax methods.

The block was trimmed on the microtome after embedding, the first section containing filter membrane was taken, and two further 6 μm sections at 50 μm and 100 μm. The sections were stained by haematoxylin and eosin in the normal manner.

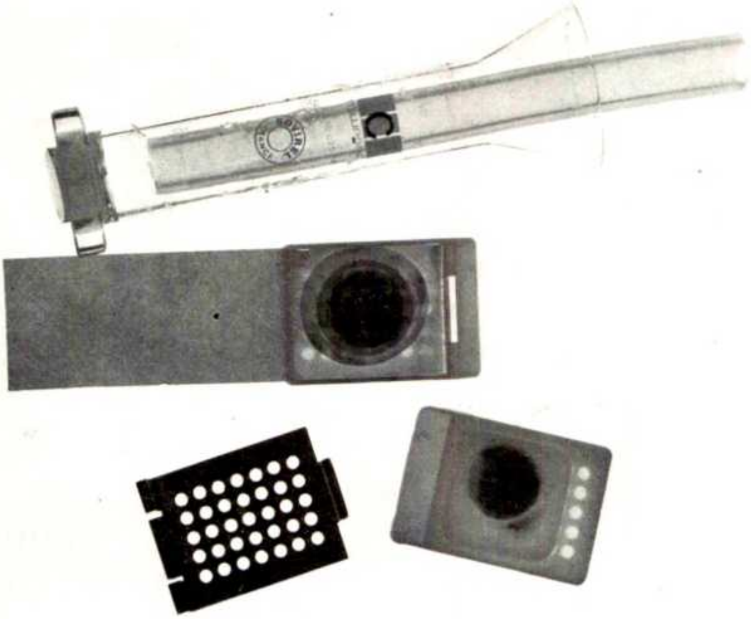

Fig. 3. The agar plug (without membrane) is partially extruded. The top cassette shows the membrane and plug in place prior to folding the filter paper over; the bottom cassette shows the appearance of the finished block

RESULTS

The filter membrane and agar block section without difficulty and microscopically were instantly recognizable. The agar appeared as a diffuse basophilic haze and the filter as a pale eosinophilic matrix.

We have found 90% of the specimen represented in the three sections taken from each block, but in none of the cases which failed to show any tumour originally did further sections produce additional information. Use of the method has shown that even where fragments of tissue were not included, the specimen was usually suitable for cytological assessment.

Tissue or cells were recovered from all 50 biopsies taken. Forty-six showed evidence of malignancy, while in the remaining four, lung tissue was obtained with no trace of tumour.

The tumours were classified according to the following scheme based on the WHO series (1967):

1. Epidermoid, including squamous and clear cell types.
2. Anaplastic; poorly differentiated, large cell and giant cell types.
3. Small cell types, lymphocytoid, oat cell, small cell undifferentiated.
4. Adenocarcinoma, with or without mucin.
5. Alveolar carcinomas, adenomatosis.
6. Malignant or atypical cells present but insufficient evidence for classification.

Items 1 and 2 and items 4 and 5 are liable to overlap.

There were 21 cases of epidermoid/squamous, four anaplastic, 10 small cell, five adenocarcinomas and six malignant/atypical cells.

DISCUSSION

The histological diagnosis in cases of solitary peripheral lesions is helpful in planning management. The introduction of aspiration needle biopsy techniques have greatly assisted and the method developed in this unit has a high success rate and can be easily carried out in most centres (Grech & Clark 1978).

At times the material obtained is small or fragmentary and processing may be difficult. For this reason the technique for treatment of small particles described here was developed. The aim of the technique was to allow concentration of fragments within a larger mass which can be processed by routine methods and prevent loss of tissue.

We were able to obtain sufficient recognizable tissue from every biopsy for histological diagnosis to be made. In 46 cases malignancy was diagnosed and in 40 histological typing of the tumour was possible. Of these 40, 15 underwent thoracotomy or came to autopsy and the histological typing was proved in 13. Both the remaining cases had malignancy, but one diagnosed as squamous cell carcinoma on biopsy had a mediastinal seminoma, and the other diagnosed as oat cell carcinoma on biopsy had Hodgkin's disease.

In 25 cases we have neither autopsy or thoractotomy evidence to confirm the histological typing but the clinical course in every case confirms the diagnosis of malignancy.

The number of cases where the histological typing was proven correct by other histology (38%) is too small to allow meaningful comment on the accuracy of classification, but it would appear that correct diagnosis of malignancy is of the order of 92%.

If the lesion is a secondary deposit and a small fragment is obtained, permitting only a cytological diagnosis, the pathologist would be unable to appreciate the *Gestalt* or pattern of the tumour essential to delineate its origin.

The types of primary lung tumour are fairly readily identifiable, i.e. small cell or squamous cell carcinoma even on small biopsies. Subgroup errors in classification are less important as the treatment is the same within the group.

Of the four cases showing no evidence of carcinoma on biopsy, one underwent thoracotomy and reactive lymph nodes with no evidence of tumour were found, two have come to autopsy with evidence of malignancy and the fourth is alive but showing progression of the lesion suggesting the presence of carcinoma.

Many series (Krumholz et al. 1966; King & Russell, 1967; Jamplis et al. 1968; Adamson & Bates 1976) have described the value of aspiration needle biopsy in providing a diagnosis, but there has been a considerable increase in our diagnostic yield following the introduction of the millipore technique (Grech 1976) for the processing of the biopsy. It has also been of value for the processing of other small biopsies, such as transbronchial lung, bone marrow and gastric biopsies.

We have restricted discussion to cases of aspiration needle biopsy where malignancy was the most likely diagnosis in an attempt to get confirmatory evidence of the histological diagnosis. The technique may be applied to any discrete peripheral lesion with equally good results, i.e. inflammatory lesions can be clearly distinguished, although the aetiological agent may not always be identifiable. In these cases unnecessary thoracotomy may be prevented.

The value of a firm histological diagnosis in the management of peripheral lesions can be considered under three headings: good risk surgical cases; border-line surgical cases and poor risk cases in which surgery is not indicated.

Good risk surgical cases

In this centre the technique is used along with bronchoscopy in the preoperative evaluation of the peripheral lesions both in planning surgery and preventing unnecessary thoracotomy. Twelve of our cases were considered to be good surgical risks and thoracotomy was offered to them all, but three refused. Eight undergoing surgery had a biopsy suggestive of carcinoma and this was subsequently proved in each case. One patient had a negative biopsy and there was no evidence of malignancy on thoracotomy. All the cases undergoing surgery are alive from 6 months to 2 years postoperatively, but two of the three refusing surgery have subsequently died.

Border-line surgical cases

The border-line group include patients who, because of age, general condition or impaired respiratory function, are likely to have a difficult postoperative period and the possibility of long-term respiratory disability. There were 14 patients in this group. The histological diagnosis assisted in management in several ways.

In cases of well differentiated squamous cell carcinoma or peripherally placed oat cell carcinoma, the surgeon may plan lobectomy or wedge resection (Morrison et al. 1963). This was the situation in five of our cases, four with squamous and one with oat cell carcinoma. In larger, more central lesions shown to be oat or small cell carcinoma, then radical radiotherapy might be considered the treatment of choice, as in six of our cases (Smart 1966; Miller et al. 1969). Three cases of large slowly growing adenocarcinoma were kept under review and referred for palliative radiotherapy when symptoms developed (Deeley & Singh 1967).

Poor risk cases

The poor risk cases include patients who, because of age, general condition or poor respiratory function, are unsuitable for surgery. In this group we have a number of cases in which the general practitioner or the patients themselves requested a firm diagnosis be made. The knowledge that the lesion is malignant may help the patient (if he wishes to know) to sort out his affairs, be useful to the relatives in adjusting to the situation, and help the practitioner managing the patient at home. There were 24 patients in this group, most of whom had few symptoms and were kept under review. Five received palliative radiotherapy for distressing symptoms.

We feel that aspiration needle biopsy has greatly assisted in the management of these patients. The technique is simple and easy to carry out with the equipment available in most X-ray departments. In district general hospitals many physicians do not have access to bronchoscopy facilities and aspiration needle biopsy of a peripheral lesion may give valuable information.

ACKNOWLEDGMENTS

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THE ASSOCIATION OF ADENOCARCINOMA OF THE LUNG AND BLASTOMYCOSIS FROM AN UNUSUAL GEOGRAPHICAL LOCATION

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Summary

A case of North American blastomycosis acquired outside the American continent and presenting with a left hilar mass is reported. The progressive hilar enlargement, despite adequate antifungal treatment, raised the possibility of drug resistance, concomitant tuberculosis and carcinoma. Non-invasive diagnostic studies including cultures, cytology and fibreoptic bronchoscopy were negative. On thoracotomy, both blastomycosis and a poorly undifferentiated adenocarcinoma were evident.

INTRODUCTION

In recent years, North American blastomycosis acquired outside the American continent has been recognized (Andleigh 1951; Emmons 1964; Galt & Ajello 1968). Little attention has been given to the coexistence of blastomycosis and other pulmonary disease and to the difficulty of making these concomitant diagnoses. The association of blastomycosis and histoplasmosis has been the subject of few reports (Allison et al. 1962; Brandsberg et al. 1964) and concurrent infection with tuberculosis has recently been stressed (Rein et al. 1974). Although the coexistence of bronchogenic carcinoma and blastomycosis has previously been alluded to (Blastomycosis Cooperative Study 1964), it remains very uncommon and has not been the subject of individual reports. We report a patient with an unusual presentation of blastomycosis, acquired in West Africa, and found on thoracotomy to have a concomitant 'scar' adenocarcinoma.

Case Report

The patient is a 43-year-old Lebanese merchant who was in good health until 14 months before admission when he developed a firm non-tender mass over the left midclavicle. He was admitted to another hospital where the mass and clavicle were excised, *Blastomyces dermatitidis* was cultured, and the patient received 0.5 g of amphotericin B over a period of 1 month. He did relatively well until 2 months before readmission, when progressive fatigue and weight loss developed. He denied any history of cough, haemoptysis or dyspnoea. The past medical history was negative.

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The patient was a native of Lebanon, a non-smoker, immigrated at the age of 37 to Liberia (western Africa) where he had worked in the clothing industry for 5 years. The mass was noted while he was in Liberia. He has never been to the American continent and denied heavy exposure to soil.

Physical examination showed a thin pale-looking man in no respiratory distress, with a temperature of 37.4° C, pulse of 104, respiration of 14, and blood pressure of 120/80 mmHg. On examination of the chest there were few crepitant râles over the left upper and middle lung fields and absence of the left clavicle. The rest of the physical examination was essentially negative.

A chest radiograph on admission revealed prominence of the left hilum with linear markings in the left upper lobe. The white cell count was 6600 with a normal differential. An initial Gram stain of the sputum disclosed Gram-negative rods and Gram-positive cocci; however, the culture was negative for bacteria. Routine blood studies revealed no anaemia and normal chemistry. Sputum cultures and stain for acid-fast bacilli and fungi were negative. A bone marrow biopsy grew no organisms. An intermediate PPD (5 TU, stabilized) was 12 mm and the patient was started on isoniazid 300 mg and ethambutol 1200 mg daily.

On the ninth hospital day a left supraclavicular lymph node biopsy revealed evidence of non-caseating granulomas containing yeast forms consistent with *Blastomyces dermatitidis*. The lymph node, however, failed to grow on culture for acid-fast bacilli and fungi. The patient was immediately started on amphotericin B, and over a period of 2 months he received a total dose of 2.5 g. During the course of therapy the blood urea nitrogen, and serum creatinine stabilized at 46 and 2.5 mg/100 ml respectively.

After a full course of antifungal treatment, and despite adequate antituberculous therapy, a repeat chest radiograph revealed further increase in the prominence of the hilum and reticulo-nodular infiltrates in the left upper lobe. On fibreoptic bronchoscopy there was evidence of external compression of the left main bronchus with no demonstrable intrabronchial lesions. Sputum cytology and bronchial washings were negative. Liver scan showed no perfusion defects. Skeletal survey revealed no bony lesions or metastases. A diagnostic left mediastinotomy was performed. Biopsies from the lung and hilar lymph node revealed the presence of an infiltrating poorly differentiated adenocarcinoma. The tumour metastasized to the adjacent hilar lymph nodes. In addition, there was distinctive granuloma spread throughout the lung biopsy, the centre of which was necrotic and rich with round bodies that stained positively with PAS and silver methenamine, typical of North American blastomycosis (Fig. 1). The tumour was in close proximity to the

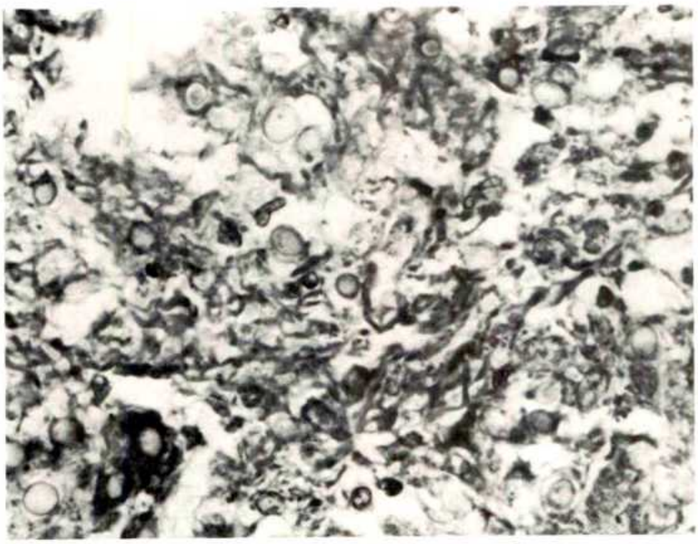

Fig. 1. Budding spores in the necrotic centre of a granuloma, typical of North American blastomycosis. PAS ×300

granuloma, in an area of scarring. The patient was advised irradiation to the left mediastinum but he requested discharge against advice.

Discussion

There is good evidence that this patient had concurrent North American blastomycosis and adenocarcinoma of the lung. The diagnosis of blastomycosis was confirmed by the initial culture and the typical histology of both the supraclavicular and hilar lymph nodes, and lung biopsy. The clinical and radiographic presentation of this man was unusual. Although the sex and age were typical, he lacked the occupational history of exposure to soil and the presence of skin lesions. Clinically he presented with a bony lesion involving the left clavicle without draining sinuses. Skeletal lesions are not rare in North American blastomycosis, reported in 75 of 174 documented cases (Black & Wilson 1953). The bones most commonly affected are the lumbar and thoracic vertebrae, pelvis, sacrum, skull, ribs and long bones of the extremities. To our knowledge involvement of the clavicle has not been previously reported. Radiologically, bone lesions are usually lytic. The development of subcutaneous abscesses in direct contiguity with a bone lesion should raise the suspicion of blastomycosis. The radiological similarities between blastomycosis and other pulmonary disease, i.e. tuberculosis and carcinoma, makes distinction between them difficult in the absence of positive cultures or cytology. Radiographically, he presented with left hilar adenopathy, an uncommon pulmonary finding in blastomycosis. Hilar adenopathy was present in 12 of 198 cases reported in the literature (Blastomycosis Cooperative Study 1964; Witorsch & Utz 1968). The rapidly growing left hilar mass with parenchymal infiltrates, despite adequate antifungal therapy, raised doubt about the underlying aetiology.

Several possibilities were considered to explain the deteriorating clinical condition. If response to amphotericin B is defined as an objective clinical improvement and inability to culture *B. dermatitidis*, the progressive clinical and radiological deterioration raised the possibility of amphotericin B resistant organism. It has been known that different fungal species do differ in their susceptibility to amphotericin B, though clinically significant drug resistance has not arisen during therapy (Bennett 1974). To our knowledge, the only report of amphotericin B resistant strains is that of two isolates of *Candida tropicalis* from a patient with funguria (Woods et al. 1974). Several workers have isolated resistant strains of various species of *Candida* in vitro by serial transfer in media containing increasing concentrations of the polyene antibiotic (Bard 1972). The several negative sputum cultures makes the possibility of drug resistance unlikely. Stronger evidence for drug resistance would have raised the possibility of adding rifampicin since it has been recently shown to enhance the effect of amphotericin B on fungi (Kobayashi et al. 1972). Simultaneous infection with *Blastomyces dermatitidis* and *Mycobacterium tuberculosis* is not uncommon and was considered. It occurred in 21 of 194 patients reported in several series and has been the subject of several individual cases (Black & Wilson 1953; Cherniss & Waisbren 1956; Rein et al. 1974). Any case of North American blastomycosis in which the patient responds only partially to antifungal therapy should be considered as a potential double infection. Search for tuberculosis in our patient failed to show acid-fast bacilli.

Since blastomycosis arising in the lung often presents as circumscribed nodules, it often simulates carcinoma clinically and radiologically. The progressive enlargement of the left hilum raised the possibility of lung cancer. This coexistence of North American blastomycosis and bronchogenic carcinoma has been briefly alluded to in one review (Blastomycosis Cooperative Study 1964), noted in three cases. The difficulty in distinguishing the pulmonary lesions of blastomycosis from carcinoma is evidenced in the Veteran's Administration study by the 19 instances in which the diagnosis of blastomycosis was made only after an exploratory thoracotomy. The patient under discussion represents the fourth reported case of blastomycosis associated with pulmonary carcinoma, thought to be arising at a scar. It has been known for many years that primary lung cancer frequently arises adjacent to scars, and such tumours are commonly called scar tumours by pathologists (Raeburn & Spencer 1957). Most scar tumours, like the present case, are poorly differentiated adenocarcinomas.

Until recently, blastomycosis has been considered a North American infection, since the source of infection has almost invariably been traced to the North American continent. Nevertheless, the geographical limitation of the disease is no longer tenable as verified cases have now been reported from Africa, Asia and South America (Andleigh 1951; Emmons 1964; Galt & Ajello 1968). The origin of this patient's infection remains unknown. Although the diagnosis was made in Lebanon, blastomycosis was probably acquired in West Africa, where the patient had spent his previous 5 years. The patient had never travelled to the American continent and denies any heavy exposure to soil. To date, there has been no reports of documented fungal disease from Middle Eastern countries. Two patients with blastomycosis previously reported from this medical centre have also acquired the fungal infection as immigrants in West Africa and Brazil (Matta & Farah 1971; Malak & Farah 1973).

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LUNG CHANGES AFTER GOLD SALTS

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Introduction

We report the case of a retired coal miner with proven rheumatoid arthritis and a past history of pneumoconiosis who developed abnormal clinical and radiological lung changes following a course of parenteral gold salts. The evidence suggests that sodium aurothiomalate (Myocrisin) was responsible.

Case Report

A 62-year-old retired miner was admitted to hospital in March 1976 with clinical signs suggestive of a pneumonia. He had first been seen in the same hospital in 1956 when, as a coal-face worker, he had a chest radiograph showing simple emphysema. In 1967 his chest radiograph showed diffuse mottling characteristic of pneumoconiosis, though not very marked. In 1975 seropositive rheumatoid arthritis affecting his wrists, hands, ankles, feet, shoulders and neck was diagnosed. His ESR was 50 mm/hour and rheumatoid changes were noted on the radiographs of his hands and feet. His chest radiograph (Fig. 1A) showed coalworkers' pneumoconiosis category I. After trying a number of anti-rheumatic drugs including aspirin, indomethacin, ketoprofen, naproxen and flufenamic acid, a satisfactory regimen comprising oral ibuprofen and indomethacin suppositories was reached. He did very well on this treatment throughout 1975. In January 1976 he began a course of weekly intramuscular injections of sodium aurothiomalate (Myocrisin). He had six 50 mg injections preceded by three test doses of 10 mg, receiving a total of 330 mg of gold salts over a period of nine weeks. These were stopped when he developed proteinuria but no other signs of gold toxicity. He continued to take ibuprofen and indomethacin as before.

About 3 weeks before the termination of this course of treatment he complained of cough and dyspnoea, followed by symptoms of general malaise, weakness, lack of appetite and a small haemoptysis. His own doctor diagnosed influenza, and when the patient developed a productive cough and signs suggesting infection in the right upper lobe he arranged a chest radiograph and treated him with oral oxytetracycline and sulphamethizole. These antimicrobials failed to produce any improvement and oral ampicillin was substituted for them. Ampicillin was likewise ineffective and cephalexin was tried briefly before the patient's admission to hospital on 26 March 1976.

On examination he was tachypnoeic at rest but not cyanosed or shocked. No finger-clubbing was noted and his temperature was normal. His blood pressure was 120/80 mmHg and pulse 96/minute and regular. There were no signs of cardiac failure and examination of his abdomen was unremarkable. He complained of a sore mouth but no oral or skin lesions were seen. Air entry was diminished and coarse crepitations were heard in the right upper lobe and in both lung bases.

The chest film showed irregular soft shadowing in both the right upper and lower lobes and some in the left lobe on a background of pneumoconiosis (Fig. 1B). His haemoglobin was 13.7 g/dl, total white cell count 16×10^9/litre, of which 4% were eosinophils, 74% polymorphs, and 22% lymphocytes. His ESR was 97 mm/hour and urea and electrolytes were within normal limits. Latex fixation test for rheumatoid disease was positive at a titre of 1 in 640. Sputum examination revealed normal flora and no tubercle bacilli were isolated. *Candida albicans* was cultured from a throat swab. Lung function tests showed a reduction by 50% from the predicted values of both FEV_1 and FVC, indicating a restrictive ventilatory defect.

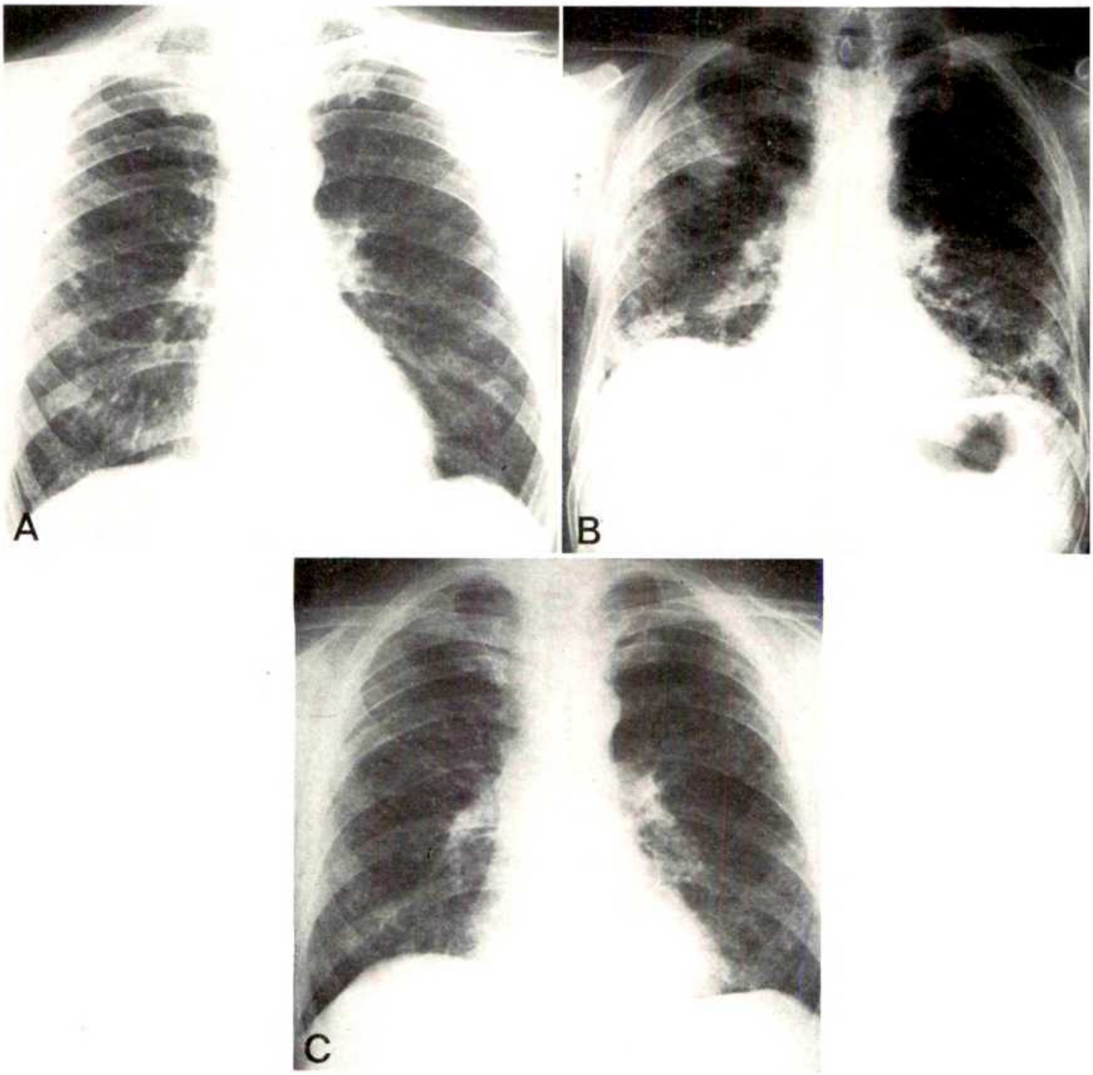

Fig. 1. Chest radiographs. A, April 1975, showing coalworkers' pneumoconiosis category 1. B, March 1976, showing abnormal shadows associated with toxicity to sodium aurothiomalate. C, Jan. 1977, showing resolution of abnormal changes

He was treated initially with oral co-trimoxazole and nystatin for 7 days but responded to neither of these agents. At this stage his respiratory illness had lasted a month and he was clearly not responding to conventional treatment. Ibuprofen was discontinued on the suggestion that he might be suffering from a reaction to this drug. A marked deterioration in the condition of his joints followed in spite of alternative therapy with fenoprofen. By 6 April the clinical and radiological state of his chest had improved sufficiently on withdrawal of all treatment save for oral fenoprofen and indomethacin suppositories to allow him home, 12 days after his admission, on these drugs.

He was reviewed at frequent intervals as an out-patient when chest X-rays and lung function tests were performed. Both these showed serial improvement.

	Predicted	*31 March 1976*	*6 May 1976*	*24 Jan. 1977*
FEV_1 (litres	2.9	1.3	1.7	2.4
FVC (litres)	3.9	1.6	2.4	3.6

On 22 June 1976 he started taking ibuprofen again after a flare-up of his rheumatoid arthritis, and on 7 July he was given prednisolone 5 mg twice daily. By this time his joints were very much better, his ESR had dropped to 24 mm/hour and his chest radiography showed further improvement. By January 1977 the clinical condition of his chest and his ventilatory function had returned to normal and his chest radiography had cleared (Fig. 1c).

DISCUSSION

We believe that sodium aurothiomalate was the cause of this man's lung disease. Our reasons are as follows. The abnormal pulmonary changes described appeared first 6 weeks after beginning a course of gold therapy. They failed to clear with five different antimicrobials. They began to resolve spontaneously after withdrawal of gold therapy and disappeared completely with the administration of prednisolone. Both ibuprofen and indomethacin, which had been taken by the patient for more than a year before his illness, were resumed after discharge from hospital, without any relapse or recurrence of the abnormal signs.

Pulmonary changes associated with rheumatoid arthritis are not uncommon. Their reported incidence varies from about 2% to 47% according to what methods of detection are used (Talbott & Calkins 1964; Frank et al. 1973; Whorwell et al. 1975). The main ones now recognized are pleural changes (*Lancet*, leader 1972), rheumatoid fibrosing alveolitis (Stack & Grant 1965), Caplan's syndrome (Caplan 1953), lung nodules (Raven et al. 1948), pulmonary infiltrations associated with pleuropericarditis (Beck & Hoffbrand 1966), arteritis of the pulmonary vessels (Gardiner et al. 1957), and an increased susceptibility to respiratory infections.

Of these respiratory manifestations of rheumatoid arthritis our case most resembles those reported by Beck and Hoffbrand (1966). They described three patients with established rheumatoid arthritis who developed acute pulmonary changes accompanied by pleurisy and pericarditis. However, none of their patients had received gold and the chest radiograph appearance of the changes they illustrate differ from the irregular mottling shown in Fig. 1B. Furthermore our patient did not have pericarditis. It is our opinion that the pulmonary changes we have described were caused by gold.

Gold salts have been used for the treatment of rheumatoid arthritis for over half a century now and their toxic effect on many tissues is well known. However in three reviews of the pulmonary complications of drug therapy (Brettner et al. 1970; Rosenow 1972; *British Medical Journal*, leader 1976) gold is mentioned once, and then only within the group of drugs causing systemic lupus erythematosus and the complications thereof (Rosenow 1972). It is also surprising how infrequently the literature on rheumatoid lung disease makes reference to therapy (Brannan et al. 1964; Talbott & Calkins 1965; Frank et al. 1973; Whorwell et al. 1975). Only recently have two reports specifically suggesting that chrysotherapy caused pulmonary damage appeared (Geddes & Brostoff 1976; Winterbauer et al. 1976). They describe three patients with diffuse reversible pulmonary injury following the administration of sodium aurothiomalate which resolved when this drug was discontinued. Our case resembles these.

In the light of this discussion we wonder how often so-called rheumatoid lung disease is in fact due to the adverse effects of therapy.

ACKNOWLEDGEMENTS

We should like to thank Joan Wilkinson for preparing the several drafts of this paper, Miss R. Shotton for photographing the chest radiographs and Dr Sarah J. Pearce for her helpful advice in its writing.

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BOOK REVIEWS

Lung Sounds

Paul Forgacs

London: Baillière Tindall. 1978. viii + 72. Price £4.50

This is a unique small book. Paul Forgacs uses plain speaking to explain the basic acoustics of the sounds generated within the chest during breathing. The brilliant simplicity of transforming the concepts propounded by Laennec into current scientific thinking, in a way that is also relevant to physicians, makes this book essential for everyone who tries to use a stethoscope. There are very few books indeed that one would expect to be possessed by every doctor, but it is no exaggeration to say that this one not only should be, but almost certainly will be, one of them.

The presentation of this book is in the style of its contents. The type setting is large and clear, and the diagrams large, simple and explicit. Good references and an adequate index enhance the value of this splendid book.

M. TURNER-WARWICK

A Diagnostic Approach to Chest Diseases: Differential Diagnoses Based on Roentgenograp'ic Patterns

Glen A. Lillington and Robert W. Jamplis

Baltimore: Williams and Wilkins. 1977. xiv + 608. Price $54.00

In this book the aim of the authors is to produce a practical approach to the diagnosis of pulmonary disease. In stating that the patient presents as a collection of symptoms, signs and investigatory findings, they point out that this frequently (though not invariably) means that the chest radiograph is abnormal. They have based their book in the categorisation of abnormal radiographic signs and their subsequent investigation. Whilst they state that the book is not primarily a radiological textbook, they have indicated how investigatory problems may be approached once the radiological signs have been established.

The book is divided int four sections. Firstly, there are three chapters outlining diagnostic techniques. These include the history and physical examination, radiological and radio-isotope studies and finally other diagnostic procedures. The second section is a brief but very clearly defined list of radiographic patterns with illustrative examples. The accompanying text enlarges on the defibition of these paterns.

The third and major section considers each of these examples in detail. A differential diagnostic list of the principal causes is presented. A more detailed description is given of these causes and the investigatory techniques which are most likely to prove useful for any particular condition are indicated. The diagnostic techniques themselves are then considered in relation to their likely usefulness. A suggested course of diagnostic management is then outlined.

In the fouth section symptoms suchas cough, signs such as haemoptysis and the syndrome of pulmonary infiltration and eosinophilia are considered in the same manner as the radiological appearances detailed in the third section.

The quality of the radiographs is excellent and the legends are informative. It would perhaps have helped if there had been more radiographs illustrating the diagnostic differences referred to in the text. Occasionally the subheadings in the text are a little difficult to pick out but these are all minor criticisms. One particularly useful feature is the list of references divided into subsections which appears at the end of each chapter. It is only to be hoped that they do not date too rapidly.

The book has been written on the basis that the problem to be solved can be identified and it has been assumed it will usually be related to an abnormal radiograph. The possible causes are indicated. The manner in which these may be identified are oulined and mdghocx by which the diagnosis can be established are suggested. This approach will surely be found invaluable by all clinicians, whether primarily chest specialists or not. It will also appeal to radiologists in that they will have a broader base on which to place their interpretation of the chest radiograph.

M. C. PEARSON

Lung Biology in Health and Disease, 2. The Biochemical Basis of Pulmonary Function

Ronald G. Crystal

New York: Marcel Dekker. 1976. xviii + 534. Price SF 150

This book starts off with a description of the many cell types which go to make up the whole lung which have been identified since the electron microscope was applied to the lung. Although the gross functions of many of these cells are well known, e.g. mucus secretion, phagocytosis, ciliary activity and so on, the activities of others are less well defibed. Indeed, this sort of study had to await the appearance of methods of obtaining concentrated and viable preparations of individual cell types; a chapter of the book is devoted to tracing the development of these methods and to descriptions of those techniques which have been found most suitable. Subsequent chapters deal with the energy requirements of lung tissue, lipid metabolism and protein synthesis in general and with certain aspects of the synthesis of specific secretions of the lung such as surfactant and prostaglandins. The development of collagen and elastin is dealt with in detail and its importance in the fibal structure of the lung and its place in determining the physical properties of the lung as a qhole. A particularly interesting chapter is devoted to α_1-antitrypsin and its effects on lung development and on the association between deficiency and emphysema. Each contributor has been at pains to point out the possible clinical bearing of the work he describes. The book concludes with a long chapter in which the relationships between the biochemistry of the lung, its structure and its functions are examined in depth.

In the past few decades, we have seen the emergence of methods which have made it possible to relate the main respiratory functions of the lung to the gross anatomy and histology in quantitative terms. It is now evident that the non-respiratory functions of the lung have also to be taken into account in the genesis of disturbed lung function and that correlations between abnormalities in these and abnormalities of cell structure and function are likely to be fruitful in understanding the mechanisms of disturbed function of the whole lung.

The book is well written and (what may be more important) very well edited. The illustrations are uniformly good and apposite without being too numerous. The price in this country is forbiddingly high and may confine the book to established libraries and institutions. Nevertheless, I can see no way of avoiding the necessity for every expert on respiration physiology to read this fascinating book.

F. J. PRIME

Fundamentals of Respiratory Therapy

Donald F. Egan

St Louis: Mosby (London: Henry Kimpton). 1977. x + 551. Price £12.60

The third edition of this will be of great value to the physiotherapist who is working in a chest hospital.

Although the first few chapters are mainly concerning academic knowledge, the remaining chapters are of excellent reading and value for clinical work.

There have been some very good additions to the third edition, such as a lengthened explanation about positive end-expiratory pressure, and paragraphs explaining fibreoptic bronchoscopy and humidification, to mention only a few examples.

I am sure this book will have a place in the physiotherapy departments of chest hospitals.

PATRICIA TOMLIN

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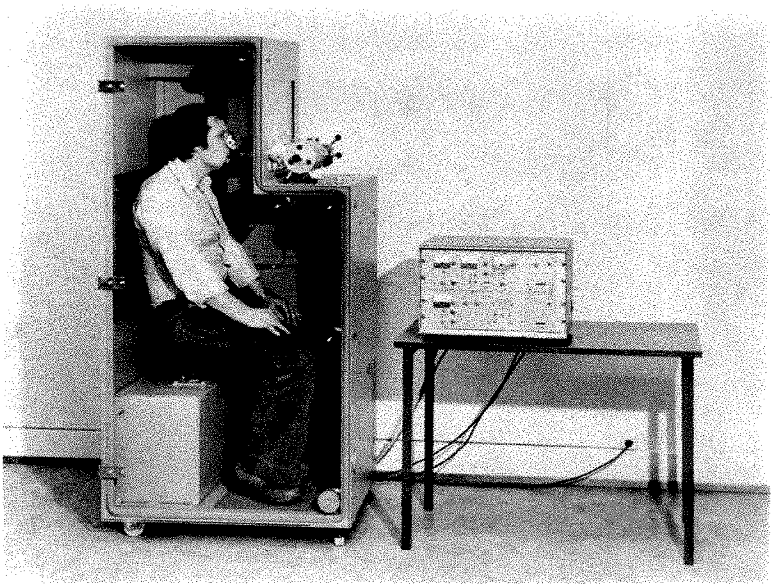

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THE BRITISH THORACIC ASSOCIATION

The 50th anniversary meeting of the association was held at the Palace Court Hotel, Bournemouth, on 19–22 April 1978. The following papers were presented.

Laboratory Diagnosis of Fungal Disease of the Lung

LESLIE MILNE

Western General Hospital, Edinburgh

Bronchopulmonary aspergillosis can be difficult to distinguish clinically from other lung diseases such as tuberculosis, carcinoma and bacterial pneumonia and infarction. Reliable laboratory methods are therefore essential in order to assist the clinician in establishing a definitive diagnosis.

The present investigation was carried out primarily to establish reliable methods for the isolation of *Aspergillus fumigatus* from sputum and secondly by applying these techniques to determine the quantities of fungus present in the sputum of known hospitalized cases of aspergillosis in relation to daily ward routines.

Sputum homogenized using pancreatin was centrifuged and the resulting sediment used for culture and microscopy. Incubation temperatures of 28, 37 and 45°C were compared and it was found that *A. fumigatus* was frequently isolated at 45°C when no growth occurred at the lower temperatures due to an overgrowth of bacteria and yeast fungi. The choice of 45°C as a selective agent enables sputum that has been stored for several days or sent by post to be successfully cultured for *A. fumigatus*.

A number of known aspergillosis patients were investigated by collecting sputum continuously for 10 days divided into 8-hourly samples. Certain trends were evident: sputum from patients with necrotizing aspergillosis generally contains high numbers of colony forming fragments in the range 1×10^3 to 1×10^6 colonies per 8-hour sample; patients with aspergilloma tend to vary from one individual to another and the range is generally from 0 to 1×10^3 colonies; the allergic group are the most erratic of all with counts going from 0 to 1×10^6 colonies. No optimum period for the collecting of sputum could be identified. A 3-day sputum collection was suggested as a means of obtaining a representative sample for laboratory diagnosis.

During routine diagnostic work it was noted that morphological variants of *A. fumigatus* were isolated on occasions. These variants tend to be slower growing and produce fewer spores than the normal or 'wild-type' isolate. So far variants have been recovered exclusively from patients with aspergilloma and they may therefore be taken as indicative of this form of aspergillosis.

The methods outlined above not only provide the basis for reliable diagnosis but also by quantitation a means of assessing the efficacy of chemotherapy. In addition the precise form of aspergillosis may be suggested. Moreover, clinicians who do not have a local specialist mycology laboratory now have the means of access to such facilities by postal service.

Inhaled Corticosteroids and Allergic Bronchopulmonary Aspergillosis

Report of the BTA Research Committee

G. K. CROMPTON

Northern General Hospital, Edinburgh

The study was designed to investigate the effect of inhaled beclomethasone on bronchial fungal colonization in patients already known to have allergic bronchopulmonary aspergillosis and to assess the efficacy of this drug in the control of asthmatic symptoms in these patients. A double-blind cross-over study was designed: 6 months beclomethasone 100 μg four times daily and 6 months placebo. Fourteen centres entered patients whose prestudy therapy was continued throughout the trial period in all cases. Exacerbations were treated according to the participating physicians' normal practice. A clinical assessment was made every month. Chest radiographs were taken every second month and during exacerbations. Patients completed diary cards every day during the 12-month period and indicated the severity of their asthmatic symptoms and volume of their sputum. Alterations in prednisolone and antibiotic therapy were recorded. Twenty-four-hour volumes of sputum were collected at monthly intervals for mycological investigation and serum specimens for quantitative estimation of precipitins to *Aspergillus fumigatus* were taken every second month.

RESULTS

To eliminate early changes before treatment had taken effect mean values were calculated for the latter parts only for each treatment period. Thirty-six patients entered the study and data were available for analysis on 32 patients.

Ventilatory function tests, symptoms and sputum scores. All these indices were better, on average, during the active treatment than in the placebo period, but there were no differences significant at the 5% level.

Changes of treatment. In the case of prednisolone no treatment was given in 19 patients, 11 received more extra prednisolone therapy during the placebo period than the active, and 2 received more prednisolone in the active treatment period. This difference was significant in favour of the active treatment ($P = 0.02$). Thirteen patients were not given antibiotic therapy, 8 received more treatment during the placebo period than the active and 7 were given more treatment during the active period. In 4, treatment with antibiotics in each period of the study was the same.

Exacerbations. These were assessed as clinical exacerbations (without radiographic deterioration) and exacerbations confirmed by an abnormal chest radiograph. Seventeen patients completed the study without a clinical exacerbation, more patients had clinical exacerbations during the placebo period than the active, but this difference was not significant. More radiographic abnormalities developed during the active period than the placebo, but again this difference was not statistically significant.

The mycological and serological data were not analysed for this preliminary report and may, therefore, influence the final conclusions. The results of this preliminary analysis indicate that the control of asthmatic symptoms was significantly better during the active treatment period with beclomethasone, but exacerbations of allergic bronchopulmonary aspergillosis are not any less frequent when this drug is given.

A Study of the Long-Term Effects of Talc Pleurodesis

Report of the BTA Research Committee

JOHN CHARLES

Llandough Hospital, Penarth

In a study of the possible effects of cosmetic talc, 210 index cases who had received talc pleurodesis as treatment for pneumothorax and other non-malignant pulmonary conditions, were collected from three thoracic centres. The study is not yet complete, but in the follow-up, which extends for up to 40 years, there has been no case of mesothelioma and no increased incidence of bronchogenic carcinoma.

The BTA Tuberculosis Contact Study

Report of the BTA Research Committee

B. H. DAVIES

Sully Hospital, Glamorgan

A standardized procedure in contacts of patients with all types of newly diagnosed tuberculosis was undertaken to assess the present relevance of contact examination in Britain. Thirty-seven clinics participated in the study; the number of index cases entered in the study was 1237; there were 4668 close contacts and 2731 casual contacts, seen at least once after notification of the index case. The yield of close contacts, newly found to have tuberculosis, is very similar for the Asian and non-Asian (mainly British) communities, namely, 3.4% and 3.6% respectively of the total close contacts examined. The yield of new cases is about three times as great as the above percentages when the index case is positive on sputum smear, and about a third as great when the index case has non-respiratory tuberculosis. Most close contacts were undiagnosed at the initial examination, but contacts of Asian index cases had an appreciable morbidity on re-examination at 1 or 2 years, as did the close contacts of smear-positive index cases of other ethnic groups. Prior BCG vaccination has a marked protective effect and chemoprophylaxis is used too infrequently in contacts at risk of active tuberculosis.

The results suggest that the tracing and examination of contacts remains a worthwhile procedure resulting in the detection of significant numbers of previously unsuspected cases of tuberculosis in the contact population. All close contacts should be examined once. Close contacts of Asian index cases with respiratory disease and close contacts of smear-positive non-Asian index cases should be examined annually for at least 2 years. BCG vaccination or chemoprophylaxis should be actively considered in these groups. Casual contacts should be examined only if there is unusual exposure to a highly infectious index case.

Comparison of Pirbuterol with Salbutamol in Asthma

Report of the BTA Research Committee

A. D. Mackay*

Southampton General Hospital

Ninety-five patients with reversible airways obstruction entered the study, which was conducted double-blind in 27 centres with random allocation to pirbuterol or salbutamol after a week on placebo. The treatments and placebo were given in identical capsules taken after meals. A cross-over of therapy took place in the final phase of the study.

The patients recorded peak flow gauge readings three times daily prior to taking the capsules. The number and timing of puffs of a salbutamol inhaler used as required for additional symptomatic relief were also recorded on a daily diary card as were self-assessments on line diagrams of dyspnoea, sleep, awareness of palpitations, steadiness of the hands and overall impression of how they felt.

Twenty-three patients were withdrawn from the study and 16 of the withdrawals were unrelated to either active drug; 3 withdrew while on placebo, 1 developed an unrelated illness and 12 failed to fulfil the protocol and were therefore excluded from the analysis. Tremor was the chief unwanted effect in the 7 who withdrew on active treatment. Analysis of the results provided by the remaining 72 patients showed no significant difference between pirbuterol 10 mg and salbutamol 4 mg each four times a day in terms of effect on peak expiratory flow rate. Similarly the patients could not distinguish between the active drugs in the subjective assessments.

A Comparison of Tine and Mantoux Tuberculin Tests

Report of the BTA Research Committee

J. A. Lunn

St George's Hospital, London

Intradermal Mantoux (5 T.U.) and Tine tuberculin tests were made at the same time on the opposite arms of 307 subjects. The results of each test were read by two independent observers at either 48 or 72 hours. Positive readings of 5 mm or more of induration were recorded for 59% of the Mantoux tests; 34.7% were of 10 mm or more. Positive readings of 5 mm or more of induration were recorded for 3.9% of the Tine tests; a further 15.5% were recorded in the doubtful category of 2–4 mm of induration.

These results indicate that the Tine test is unsuitable as a single test for epidemiological use because of the high proportion of negative and doubtful results in individuals positive to the Mantoux test. For the same reasons its usefulness in clinical practice is very limited.

Treatment with House Dust Mite Extract in Bronchial Asthma

Report of the BTA Research Committee

S. Lal

Bury General Hospital

Patients with asthma, considered to be due to house dust mite allergy, were allocated at random to treatment with (*a*) increasing weekly injections of house dust mite extract for 18 weeks followed by monthly injections to complete 18 months of treatment, (*b*) similar injections for 18 weeks followed by placebo injections up to 18 months, or (*c*) placebo injections for 18 months. fifty-six patients completed at least 6 months of observation.

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* BTA/CHSA Research Fellow.

In patients not on corticosteroids, the treated group did a little better than the controls as judged by night asthma scores, discontinuation of bronchodilators and overall blind assessment of the records by a panel of independent physicians. No benefit was apparent by extending treatment from 18 weeks to 18 months. In contrast, patients on corticosteroids given placebo injections did a little better than the treated group.

The extract used was stronger than the commercially available preparation and the injections had to be stopped in one-sixth of the patients because of side effects. The improvement in patients not on corticosteroids in this trial was of doubtful value.

Bronchial Artery Embolization in the Control of Massive Haemoptysis

D. MacErlean and M. X. FitzGerald

St Vincent's Hospital, Dublin

Therapeutic embolization of arterial channels has recently been introduced in a wide variety of clinical settings. These include embolization to abort life-threatening bleeding or to obliterate vascular tumours or arteriovenous anomalies. This paper reported experience with embolization of the bronchial arterial supply in a patient with recurrent severe haemoptysis secondary to bleeding from an upper lobe aspergilloma. The methodology, hazards and therapeutic implications of this technique were discussed.

Computerized Tomography of the Thorax

D. Katz

Northwick Park Hospital

Computerized tomography (CT) has created a new dimension in the radiology of the thorax. Not only are the tomographic sections displayed in the axial plane but, because of the high sensitivity of the recording apparatus, very small differences in tissue attenuation can be recorded and displayed and soft tissue structures not seen on conventional radiographs are easily visualized.

Many aspects of thoracic disease can now be displayed at an earlier stage than was possible previously. This is particularly true in pleural and subpleural areas and in the mediastinum.

An indication of the sensitivity of CT is in the detection of pulmonary metastases. Because of the predominantly subpleural distribution of metastases it is difficult to detect them early with conventional tomography due to poor surrounding contrast. CT has no such difficulty and early metastases are well seen far earlier than with conventional radiology. This has obvious advantages with regard to treatment planning in malignant disease.

It is appropriate to consider a disease process such as asbestosis which has pleural and parenchymal manifestations. An initial study of asbestosis patients with CT has shown that interstitial fibrosis was seen earlier, was more easily visible and appeared grosser than on chest films. The same applied to pleural plaques, pericardial and diaphragmatic irregularities and pleural calcification.

CT has greatly simplified the detection of lymph node disease within the mediastinum. Both retrosternal and mid-mediastinal lymph node enlargement is easily and clearly displayed and greatly simplifies the staging of disease, therapy planning and the monitoring of response to therapy.

Initial work has demonstrated many other examples of the sensitivity of CT and it is now obvious that many diseases including bullae, pleural effusions, pulmonary oedema and thoracic wall tumours can be detected earlier and more readily with this new diagnostic tool.

Immunoglobulin E Levels and Clinical Status in a Group of Asthmatic Patients

W. D. Linehan

Mater Misericordae Hospital, Dublin

Sixty asthmatic patients were examined. They were a mixed group of different ages and different types of asthma. Their clinical status was divided into five groups from mild to severe depending on response to treatment.

Blood eosinophilia, skin allergy and air flow tests and total serum levels of IgE were performed and repeated. The clinical grading of each patient was matched against his or her IgE levels. The value of these tests were discussed in the clinical situation of ordinary management and prognosis and in the cost/benefit situation.

Respiratory Disease in an Electronics Factory

W. H. PERKS, P. S. BURGE, J. PEPYS
AND M. GREEN
Brompton Hospital, London

Twenty-two workers with asthma in an electronics factory have been described and it was shown by occupation type provocation tests that their symptoms were due to the colophony fumes from heated solder flux (Burge et al. 1977). The personnel and medical departments at the factory had no knowledge of any occupational respiratory disease. We wondered, however, if respiratory symptoms might be commoner than suspected, and conducted a survey of the workforce.

Analysis of 1338 leaving records over the previous 3½ years showed that significantly more employees left the shop floor (where soldering took place) for health reasons than left stores or office, and this difference was attributable to work-related respiratory disease in the solderers.

532 employees answered a questionnaire and performed spirometry. Respiratory symptoms were more common on the shop floor than stores/office and in many improved away from work; 22% of shop floor workers complained of dyspnoea or wheeze improving at the weekend compared to only 6% of stores/office workers. Spirometry revealed that the FEV_1 of shop floor workers (93.8% predicted) was significantly less than of stores/office workers (100.2% predicted).

50% of the employees known to have colophony sensitivity (by in-patient bronchial challenge testing) in the survey showed a 10% fall in FEV_1 during the working day. Similarly 31% of shop floor employees with respiratory symptoms improving at the weekend (but not formally challenged) showed a 10% fall in FEV_1, compared to only 6% of symptom-free shop floor controls. Symptomatic employees more commonly had raised serum levels of IgE and positive skin 'prick' tests to common allergens.

The results of the survey suggest that solder flux asthma is a widespread problem in this electronics factory. The fact that it was long unrecognized suggests that other factories may be similarly affected.

BURGE, P. S., GREEN, M. & PEPYS, J. (1977) Occupational asthma due to sensitivity to colophony (pine resin). *Am. Rev. resp. Dis.* *115*, 203.

Phage Typing of Tubercle Bacilli

JOHN M. GRANGE
Cardiothoracic Institute, London

Bacteriophage typing has been used to subdivide *M. tuberculosis* for epidemiological purposes since 1966. At present there are four major types: A, B, C and I with further subdivisions by so-called auxillary phages. Several workers have demonstrated marked geographical variations in the distribution of these types, notably between Great Britain and India.

In recent years there has been a marked increase in the incidence of tuberuclosis among immigrant Asians in Great Britain, many of whom have extrapulmonary manifestations of the disease with widespread lymph node involvement being very common. The distribution of phage types among these Asian patients was very similar to that found previously in India but significantly different to that found among indiginous British patients. In particular, many strains from Asians were phage type I, a type infrequently found among British patients. Recent co-operative studies* have shown that strains of phage type I differ from other human strains in being attenuated for the guinea-pig, susceptible to hydrogen peroxide and to 2-thiophene carboxylic acid hydrazide and showing differences in the cell wall lipid structure. These strains may therefore represent a distinct subspecies within *M. tuberculosis*. No significant correlations between phage types and presentation of disease in man have yet been found.

In addition to studies on the geographical distribution of *M. tuberculosis*, phage typing has been successfully used to confirm epidemiological links in small groups of patients, to distinguish between reactivation and reinfection following therapy and to differentiate

* These studies were performed in co-operation with Professor D. A. Mitchison and his colleagues (MRC Unit for Laboratory Studies in Tuberculosis) and Dr M. B. Goren (National Jewish Hospital, Denver, Colorado, USA).

BCG from virulent human and bovine strains. The future development and usefulness of phage typing will depend on close cooperation and communication between laboratory workers and those involved in the clinical aspects of tuberculosis control.

Short-Course Daily and Intermittent Regimens in Treatment of Newly Detected Pulmonary Tuberculosis

M. Zierski

National Research Institute for Tuberculosis, Poland

Four daily and intermittent regimens with isoniazid (INH), rifampicin (RMP) and ethambutol (EMB) were applied in nearly 370 patients, mostly severely ill and heavily sputum smear-positive. At the end of 6 months of treatment they appeared similarly highly effective, with a 100% sputum culture conversion rate. Initially all patients were treated daily with triple drugs for 8 weeks in hospital and afterwards continued supervised treatment as out-patients in four random groups. One group received therapy daily for 6 months; the others received a double or triple drug combination twice weekly or a triple drug regimen once weekly. 10% of bacteriological relapses were observed in nearly 250 patients who had a 24-month follow-up after completing the 6 months of chemotherapy. No statistical significant differences were noted in the rates of relapses. The bacteriological relapses occurred mainly in the first year after completing treatment; all patients had bacilli sensitive to previously used drugs. It can be concluded after the preliminary analysis of the results, that some patients suffering from advanced pulmonary tuberculosis with concomitant disease, such as cystic fibrosis, diabetes, gastrointestinal disorders and, particularly, chronic alcoholism, are at higher risk of relapses. For them a 6 month course of chemotherapy has some limitations, despite the fact that nearly 90% of all patients achieved remission of disease at 2 years with short-course chemotherapy.

East African/MRC Study of Five Four-Month Regimens of Chemotherapy

Janet Darbyshire

Brompton Hospital, London

The effectiveness of 6-month regimens of chemotherapy for pulmonary tuberculosis has been established in studies in East Africa and many other parts of the world. A pilot study of streptomycin, isoniazid and rifampicin for 3 months had an overall relapse rate of 13%. The present study is investigating the effect of both adding pyrazinamide (already shown to be an important drug in short-course chemotherapy in studies in East Africa and Hong Kong) in the initial intensive phase and prolonging the duration of chemotherapy to 4 months. Under programme conditions in developing countries standard duration chemotherapy usually achieves relatively low levels of success, sometimes of the order of 60–70%, but often lower. Even if 4-month regimens were not uniformly successful, they might still be a major therapeutic advance in developing countries, with limited resources.

Five four-month regimens were studied, all with a 2-month intensive phase followed by a 2-month continuation phase. In the first four regimens the initial 2-month phase was with streptomycin, isoniazid, rifampicin and pyrazinamide. The 2-month continuation phase was: (1) isoniazid, rifampicin and pyrazinamide, (2) isoniazid and rifampicin, (3) isoniazid and pyrazinamide, or (4) isoniazid alone. In the fifth regimen streptomycin was omitted, producing an entirely oral regimen, with isoniazid, rifampicin and pyrazinamide for 2 months followed by isoniazid alone for 2 months.

The results, including relapse rates up to 6 months after stopping chemotherapy, were presented.

Singapore Tuberculosis Service/MRC Study of 6-month and 4-month Regimens of Chemotherapy in the Treatment of Pulmonary Tuberculosis

D. J. Girling

Brompton Hospital, London

Chinese, Malay and Indian patients with sputum culture-positive pulmonary tuberculosis were treated with 2 months of daily streptomycin, isoniazid, rifampicin and pyrazinamide, followed either by daily isoniazid, rifampicin and pyrazinamide (SHRZ/HRZ regimen), or by daily isoniazid and rifampicin (SHRZ/HR regimen), allocated at random. Both regimens were given for a total duration of either 6 or 4 months, at random. The drug dosages were streptomycin 0.75 g, isoniazid 300 mg, rifampicin 450 or 600 mg and pyrazinamide 1.5 or 2.0 g, the larger dosages of rifampicin and pyrazinamide being given to patients weighing 50 kg or more.

All 331 patients with drug-sensitive strains of tubercle bacilli before treatment had a favourable bacteriological response during chemotherapy. During the first 6 months after the end of chemotherapy there have been no bacteriological relapses among 123 patients treated for 6 months who are available for assessment. In contrast, 7 (10%) of 67 SHRZ/HRZ and 5 (8%) of 66 SHRZ/HR patients treated for 4 months have relapsed. Of 32 patients with bacilli resistant to isoniazid, to streptomycin or to both these drugs before treatment, only 1 had a bacteriologically unfavourable response during chemotherapy and only 1 has so far relapsed. Of 397 patients, 11 (3%) had one or more of their drugs terminated on account of adverse reactions.

Cefuroxime in the Treatment of Lower Respiratory Tract Infections

R. P. Bax, A. F. Dawson, B. M. Mullinger and C. H. Dash

Royal Northern Hospital, London,
and Glaxo Ltd.

Cefuroxime is a new parenteral antibiotic with a wider spectrum of activity than earlier cephalosporins and is particularly active against *Haemophilus influenzae*, even strains resistant to ampicillin due to β-lactamase production. Cefuroxime is also highly effective against the great majority of other potential chest pathogens. Levels above the minimum inhibitory concentrations for *Haemophilus influenzae* and *Streptococcus pneumoniae* are achieved in the sputum within 1 hour of the first injection. Higher levels occur after subsequent injections. Serum levels above the MIC for these bacteria are maintained for over 6 hours.

Two hundred and seventy-five patients from 18 centres have been treated with cefuroxime using the standard regimen of 750 mg 8-hourly by intramuscular injection. All investigators used an identical record form and similar protocol. The clinical diagnoses were: bronchopneumonia (105), postoperative pneumonia (74) and acute exacerbations of chronic bronchitis (96). Renal function was closely monitored during therapy. In no patients were there any adverse changes in renal function attributable to cefuroxime therapy, including 17 patients who also received frusemide. Two patients (0.7%) developed a rash, although 8 penicillin-sensitive patients were treated without incident.

Of the 128 patients who had sputum cultured before and after treatment, no pathogens were isolated from 36. Bacteria were eradicated in 70 patients. The clinical results were: 90% success rate in bronchopneumonia, 91% in postoperative pneumonia and 89% in acute exacerbations of chronic bronchitis.

From these studies, it can be concluded that cefuroxime 750 mg 8-hourly is effective in the treatment of lower respiratory tract infections and offers several advantages over existing therapies.

Cystic Fibrosis: Recent Developments in Children

Margaret Mearns

Queen Elizabeth's Hospital
for Children, London

Forty years ago cystic fibrosis was first recognized as a distinct clinical entity and is now acknowledged to be the most common physically handicapping disease of childhood. Survival rate has improved and will be illustrated by the study of 151 patients born before 1964.

The most common signs and symptoms were described and some recent suggestions in management discussed. The incidence of staphylococcal infection at initial examination in the first 50 patients (1950–8) seen was compared with that of the last 50 patients seen (1973–7).

In the majority survival is dependant on the degree of pulmonary involvement. Studies were presented which demonstrate that there is disorder of pulmonary function even in patients free of respiratory symptoms.

The study of the pattern of growth during childhood was shown and indicated that although there is pancreatic dysfunction the majority of patients are not dwarfed, but there is marked delay in the onset of puberty in some patients. The endocrine status of a group with the most severely delayed puberty was presented.

Cystic Fibrosis: Clinical Aspects in Adults

JOHN BATTEN
Brompton Hospital, London

Now that the mean survival of patients with cystic fibrosis is at least 15 years, increasing numbers of patients are coming under the care of thoracic physicians. The experience in the management of over 150 patients is described; 45 of these have been intensively studied over an average of 4½ years (their average age on entry to the study was 17 years). The diagnosis of the atypical case presenting late with mild symptoms was discussed and particular emphasis placed on the problems associated with analysis of the sweat sodium concentration.

At least two-thirds of patients who reach adolescence have established bronchopulmonary infection: so far chemotherapy has failed to prevent progressive disease associated with persisting bacterial infection. The development of pneumothoraces in about 20% of patients and haemoptysis in over 50% of patients was discussed in relation to their management. While the gastrointestinal tract was shown to present few problems, the development of meconium ileus equivalent may at times present extreme difficulty in management. Overt diabetes mellitus which develops in about 10% of patients and portal hypertension, rather less commonly, was also described. The psychological consequences of progressive disease often associated with retarded growth and development and sterility in the male and the impact on the family requires a high degree of sympathy and understanding on the part of all the medical staff involved. Despite considerable advances little progress has been made in modifying the natural history of the disease during the last decade.

Genetic Heterogeneity in Cystic Fibrosis

MARGARET E. HODSON
Brompton Hospital, London

Cystic fibrosis is thought to be inherited in the classical Mendelian recessive manner. The affected individual is said to inherit two identical abnormal genes, one from each parent. However, clinical variation in the severity of the disease is well known.

Work on fibroblast cultures and cystic fibrosis factor has in recent years increased the speculation that there is a genetic heterogeneity within the disease. A joint study has been performed between Brompton Hospital and Cornell Medical Centre on an adult patient population. Staining of fibroblasts, cystic fibrosis factor assays and cellular cooperation studies have been undertaken.

Evidence was presented that there may be at least three ways in which cystic fibrosis can be inherited. The results of a family study including 49 members were described to show how a clinically mild variant of the disease may be inherited.

Lung Function in Young Children in Health and Disease

A. D. MILNER
Nottingham University Medical Centre

Little is known about pulmonary physiology in health and disease between the ages of 3 months and 5 years, as these children are too young for the methods available for studying the older child and adult and too old to accept the techniques used in the neonatal period. Recently a method has been developed to assess airways obstruction, using a modification of the forced oscillation technique which is effort-independent. This and the Wright lower-range peak flow meter can be used without sedation down to the age of 2 years 9 months. Under this age data can be obtained after sedation using the forced oscillation technique and total body plethysmography.

Using these techniques we have found that:

1. Acute airways obstruction due to acute bronchiolitis or acute wheezy bronchitis is not relieved by either β- or α-adrenergic stimulants. This is in contrast to acute laryngotracheitis which does respond temporarily to α-stimulants.
2. Acute airways obstruction due to wheezy bronchitis does respond to β-adrenergic stimulants by the age of 18–20 months.
3. Children with wheezy bronchitis between the age of 2 years 9 months and 5 years exhibit exercise-induced bronchoconstriction identical to that seen in the older asthmatic child. This can be relieved by β-adrenergic stimulants and blocked by sodium cromoglycate.

Further work is required to identify why infants failed to respond to β-adrenergic stimulants, and to assess other therapeutic agents such as parasympathetic blocking agents and xanthine drugs in this important age group.

Associations between Housing Conditions, Smoking Habits and Ventilatory Lung Function in Men with Clean Jobs

F. V. Rasmussen

University Hospital, Copenhagen

From a population study a group of 218 men with minimal occupational exposure to dusts, fumes, temperature variability or physical exertion were drawn.

The relationship between housing conditions throughout life and lung function, expressed as FEV_1, MMEF and single breath nitrogen test was analysed, with control of differences in smoking habits.

It was found that years spent in dwellings without central heating was significantly inversely associated with level of FEV_1 and MMEF, and significantly directly associated with closing capacity as a percentage of TLC. These associations were independent of smoking habits. Significant dose–response relationships between smoking habits and FEV_1, MMEF, closing capacity and slope of alveolar plateau, slope III, was found. Closing volume as a percentage of VC was only correlated to age.

These data support the hypothesis that poor dwelling conditions during childhood and adolescence, as an aspect of socioeconomic status, are associated with one or more ill-defined risk factors for development of expiratory airflow obstruction of middle age.

The analysis presented evidence that comparisons of ventilatory lung function between different occupational cateogries are insufficient and might be misleading, if housing conditions are not taken into consideration.

Chest Disease and Immunodeficiency Syndromes

A. D. B. Webster

Northwick Park Hospital

Patients who have a primary or secondary failure to make antibodies usually suffer from recurrent respiratory infections which lead to bronchiectasis. The offending organisms are usually *Haemophius influenzae* and pneumococci. Meticulous management involving antibiotics, gammaglobulin injections, plasma infusions and physiotherapy can prevent structural lung damage. The relative merits of these procedures were discussed.

A small number of patients with primary hypogammaglobulinaemia develop a condition resembling sarcoidosis which may respond to steroids. Fibrosing alveolitis may also occur. The aetiology and management of these rare complications were discussed.

Infants who have a severe defect in both humoral and cellular immunity (severe combined immunodeficiency) are prone to bacterial, fungal and protozoal lung infections. Prophylactic treatment for such infections is very important until the underlying condition can be corrected by bone marrow transplantation.

The lung conditions complicating the primary defects in polymorph function, particularly chronic granulomatous disease, and defects in the complement pathway were also described.

Patients with primary immunodeficiency provide us with some insight into the relative importance of various components of the immune system in protection against lung infections. This was discussed in the light of our present knowledge of the bronchial-associated lymphoid tissue (BALT).

Ventilation/Perfusion Scintigraphy in Patients with Chronic Obstructive Pulmonary Disease

P. Strung, P. B. Frederiksen and J. W. Rasmussen

University Hospital, Odense

Thirty-two patients admitted during a 3 month period with chronic obstructive pulmonary disease or dyspnoea due to other causes took part in a study including general history, physical examination, blood gas analyses, pulmonary function tests, chest radiographs, and ventilation/perfusion scintigraphy using the same radionuclide (^{99m}Tc-MAA) and a gamma camera for imaging.

The radionuclide lung images were evaluated by one observer only without knowing the clinical diagnosis or the laboratory results including chest radiographs. The ventilation images with a uniform distribution of the radionuclide were interpreted as normal, whereas non-uniformity was abnormal and indicated a further evaluation depending on the hypo- and/or hyperdeposition of the radionuclide activity. It was possible to grade the abnormal images into 4 groups.

The patients were ranked according to the value of $FEV_1/VC\%$, and a good correlation was seen between low ratios and grade 3 and 4. In mild degrees of chronic obstructive pulmonary disease aerosol images were more positive than the results of pulmonary function tests.

The perfusion images showed only abnormal findings in grade 3 and 4, and gave no help in evaluation of mild cases of chronic obstructive pulmonary disease. A great discrepancy was found between the aerosol images and the chest radiographs.

A further study is going on as aerosol scintigraphy seems to be a sensitive tool in diagnosing even early chronic obstructive pulmonary disease.

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Review Article

BIOCHEMICAL MARKERS IN BRONCHOGENIC CARCINOMA

R. C. Coombes, M. L. Ellison and A. M. Neville

Unit of Human Cancer Biology, Ludwig Institute of Cancer Research (London Branch), in conjunction with the Department of Medicine, Royal Marsden Hospital, Sutton, Surrey

Recent experience in the management of some tumours, in particular choriocarcinoma and gonadal tumours, has demonstrated the value of biochemical markers. With the advent of more effective chemotherapy and radiotherapy in bronchogenic carcinoma it has become apparent that such biochemical tests of disease activity would be of immense benefit in this desease also. They would be of assistance not only in mass screening but also in the differential diagnosis of pulmonary tumours. In addition to diagnosis a 'tumour index substance' could serve as an adjunct to staging and to early prediction of recurrence of tumour postoperatively. It is likely that chemotherapy is more effective when the tumour load is small and sequential monitoring would enable chemotherapy to be given much earlier in the evolution of metastatic disease.

In man tumours of every cell type can be accompanied by biochemical abnormalities in the peripheral blood or urine. Most of these abnormalities are specific neither for tumours nor for diseases of the particular organ, but there are a few quantitative and qualitative abnormalities that are more frequently demonstrable in patients with particular forms of cancer. Most often these have been detected because of the effects they produce. Tumours of endocrine glands and their secretions are the prime examples.

With the advent of more sensitive biological and immunological methods of detecting circulating and stored components of human tumours, many materials have been found in abnormal concentrations in plasma of patients with cancer and often no clear function for these materials has been defined, either in the tumour or in the host. The prime example of this is the carcinoembryonic antigen (CEA) of Gold and Freedman (1965).

We have classified the biochemical 'markers' in malignancy into three main groups (Table I). Thus, the 'products' supposedly originate from the tumour cells, as opposed to 'associated changes' that derive from functional or structural alterations to surrounding structures; included in this latter group are the changes in plasma proteins that occur in response to the presence of tumour cells. The third group includes the 'tumour-specific' bronchogenic carcinoma antigens.

Tumours of each organ have their own particular commonly associated products as changes detectable in urine or plasma. Bronchogenic carcinoma is familiar to most clinicians as being associated with various 'non-metastatic' syndromes; Cushing's syndrome, hypercalcaemia, inappropriate antidiuresis and hypertrophic pulmonary osteoarthropathy are a few of the many well-described complications which can all disappear on primary tumour removal. There are, however, more important effects of the tumour which frequently decide the fate of the patient, such as the capacity to invade soft tissue

Table I. Biochemical markers in human bronchogenic carcinoma

TUMOUR-DERIVED PRODUCTS	
Hormones	Adrenocorticotrophin (ACTH)
	Lipotrophic hormone (LPH)
	Melanocyte-stimulating hormone (MSH)
	Parathyroid hormone (PTH)
	Human chorionic gonadotrophin (HCG)
	Human placental lactogen (HPL)
	Glucagon
	Insulin
	Vasoactive intestinal polypeptide (VIP)
	Calcitonin
	Thyroid-stimulating hormone (TSH)
	Growth hormone
	Antidiuretic hormone (ADH)
	Oxytocin; neurophysin
	Prolactin
	Erythropoietin
	Serotonin
	Releasing factors
Oncofetal antigens	Carcinoembryonic antigen (CEA)
	Alpha-fetoprotein (AFP)
	γ-Fetoprotein
	β-Oncofetal antigen (β-OFA)
	Ferritin
Enzymes	Sialyl transferase
	Galactosyl transferase
	Placental alkaline phosphatase (PLAP)
Cell-turnover products	Polyamines
	Pseudouridine
	Dimethylguanosine
	1-Methylinosine
	DNA and DNA-bearing proteins
TUMOUR-ASSOCIATED CHANGES	
Glycoproteins, globulins and acute-phase proteins	β_2-Microglobulin
	Pregnancy-associated macroglobulin (PAM)
	α_1-Acid glycoprotein (AGP)
	Haptoglobin
	Haemopexin
	Caeruloplasmin
	α_1-Antitrypsin
	C-reactive protein (CRP)
Hydroxyproline	
Liver-related enzymes	
TUMOUR-ASSOCIATED ANTIGENS	
	'Specific' bronchogenic carcinoma antigens
	Leucocyte adherence inhibition (LAI)

and bone, to metastasize and to induce capillary growth and tumour vascularization. The mediators of these effects are still largely unknown, although some studies are being currently undertaken to elucidate their nature (Folkman et al. 1970; Powles et al. 1973; Easty & Easty 1974).

TUMOUR-DERIVED PRODUCTS

Hormones

The production of polypeptide hormones by non-endocrine tumours is becoming more frequently recognized as more sensitive methods for hormone detection become available (for review see Rees 1975). The reason for the frequent association with bronchogenic carcinoma is not known although there are endocrine cells termed 'Kultschitzky cells' in the bronchial epithelium (Feyrter 1954). The cells have the ultrastructural appearance of endocrine cells with characteristic electron-dense granules, a typical Golgi apparatus and staining characteristics. These cells possibly take part in the neoplastic process to a greater or lesser extent depending on the site, stimulus and histological type of tumour, and in this way their presence could account for some tumours' endocrine characteristics.

Adrenocorticotrophic hormone (ACTH). The list of hormones associated with bronchial tumours is extensive (Table I) but ACTH is the best-documented peptide. Meador et al. (1962) first demonstrated the hormone in tumour tissue and this has since been adequately confirmed in the ectopic ACTH syndrome (Ratcliffe et al. 1972). Controversy exists, however, about the significance of the peptide in tumour tissue from patients without clinical evidence of steroid abnormalities, and it is possible that it simply reflects a low level of ACTH production throughout the lung or possibly uptake of peptide by the tumour cells.

In many cases documentation is inadequate, sometimes consisting of reports of elevated peripheral levels of a hormone in association with a bronchogenic tumour. Thus, Azzopardi and Williams (1968) have rejected 25% of the reports of 'ectopic adrenocorticotrophic (ACTH) syndromes' because of inadequate documentation. Peripheral levels of ACTH are non-specifically elevated in chronic airway obstruction and other pulmonary conditions. Two detailed studies of the association between ACTH and bronchogenic carcinoma have been published. One (Gewirtz & Yalow 1974) reported significant amounts of ACTH in almost all lung tumours examined. These authors also made the important observation that lungs of 'smoking dogs' contained high concentrations of the hormone. Most of the extracted material corresponded to a higher molecular weight than native ACTH. The second major study (Bloomfield et al. 1977) contains extraction data on 14 unselected bronchial tumours not associated with the ectopic ACTH syndrome. Significant quantities of ACTH were found in all the carcinomas and oat-cell tumours but two squamous-cell and two anaplastic tumours contained insignificant quantities of ACTH.

Concerning plasma levels of ACTH, it appears that up to 53% of patients with lung cancer have raised plasma levels (Fig. I). A recent communication (Yalow et al. 1977) indicated that 24 of 36 (67%) had high ACTH levels compared with 6% of a control group. These concentrations fell after surgery and the level was related to tumour bulk.

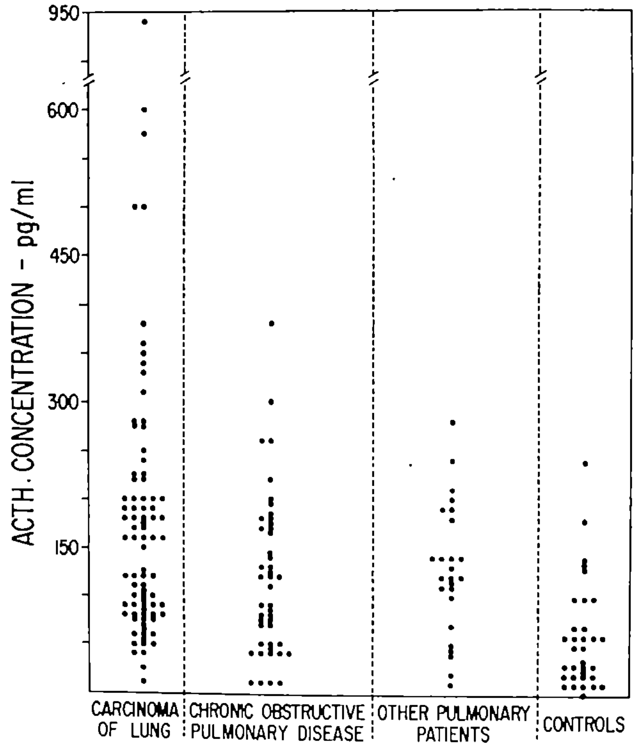

Fig. 1. Plasma immunoreactive ACTH concentrations in afternoon plasma specimens from patients with carcinoma of the lung, chronic bronchitis and other pulmonary patients and controls. (*From Gewirtz & Yalow 1974*)

However, median survival in patients with extensive disease was unrelated to initial plasma ACTH.

Future studies, presumably aimed at elucidating any chemical differences between 'native' and 'tumour' ACTH, will help to clarify the role of this hormone as a tumour index substance. Recent reports indicate that a relationship exists between big ACTH and the lipotrophin series of peptides and thus these hormones are likely to be found in bronchogenic carcinomas. Indeed, α- and β-lipotrophic hormones are often found in these tumours (Rees 1975).

In collaboration with Dr L. Rees, we have measured both ACTH and calcitonin in a variety of bronchial tumours, including one hepatoma (Fig. 2). It can be seen that, in this small series, the calcitonin and ACTH content may related.

Calcitonin. The place of the radio-immunoassay for calcitonin in medullary carcinoma of the thyroid is clearly established and the majority of patients with this tumour have high circulating levels of the hormone.

In 1970 Milhaud extracted the hormone from a bronchial carcinoid and these patients' plasmas can contain excessive quantities of the hormone, along with 5-hydroxy-

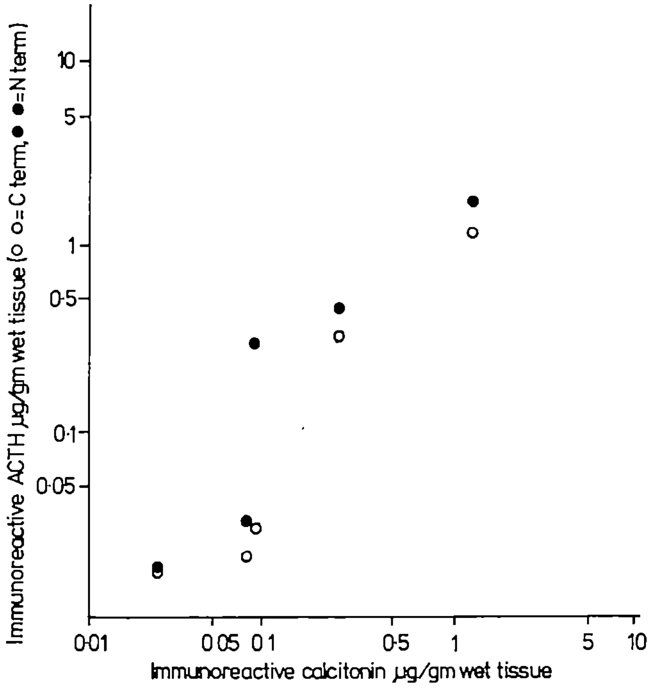

Fig. 2. Relationship of tumour calcitonin content to ACTH content in non-endocrine tumours. All these tumours with one exception were bronchogenic tumours. Calcitonin and ACTH were extracted by standard procedures (Lyons 1937; Moseley et al. 1968) and the content of each peptide measured by radio-immunoassay. ○ = ACTH content using 'C-terminal' antisera; ● = ACTH content using 'N-terminal' antisera. (Extractions of ACTH carried out by Dr L. Rees)

tryptamine and ACTH. In 1974, following a report by Silva et al. (1973), we observed that a high proportion of patients with oat-cell bronchogenic carcinoma had high levels of the hormone (Coombes et al. 1974) and subsequently showed that the tumours were capable of calcitonin production when we described a cell line derived from a poorly differentiated bronchogenic carcinoma that had been synthesizing calcitonin in vitro for more than 2 years and for over 100 subcultures (Ellison et al. 1975) (Fig. 3). The material produced by this cell line appeared to be immunologically distinct from the monomeric form of calcitonin (Fig. 4). Chromatography indicated that the calcitonin had a larger molecular weight than the monomeric form of the hormone (Coombes et al. 1976*a*) and only after incubation with trypsin did it appear to break down into the monomeric form of the hormone (to be published). Hopefully, radio-immunoassay employing this form of calcitonin will be useful in a monitoring capacity.

Although chemical studies may well be of assistance in defining more suitable antigens for monitoring bronchogenic carcinoma, work from our laboratory and elsewhere has indicated that the study of hormone-producing bronchogenic tumours in vitro can also provide much useful information.

Thus, the qualitative release of calcitonin from a bronchial carcinoma cell line in

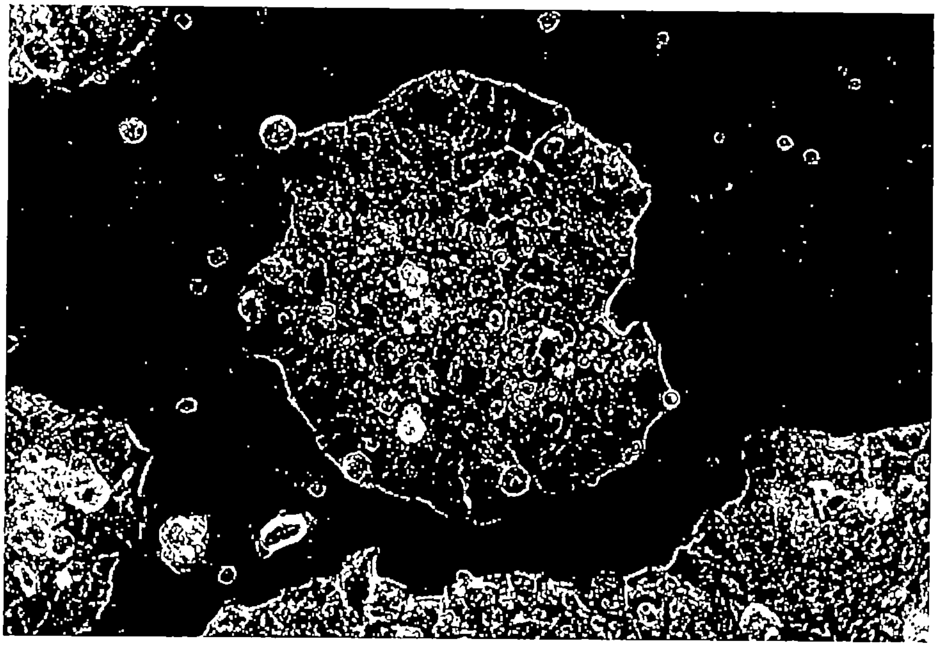

Fig. 3. Monolayer culture of poorly differentiated bronchogenic carcinoma (the 'Ben' cell-line). Islands of cells attached to the plastic surface and released CEA and calcitonin

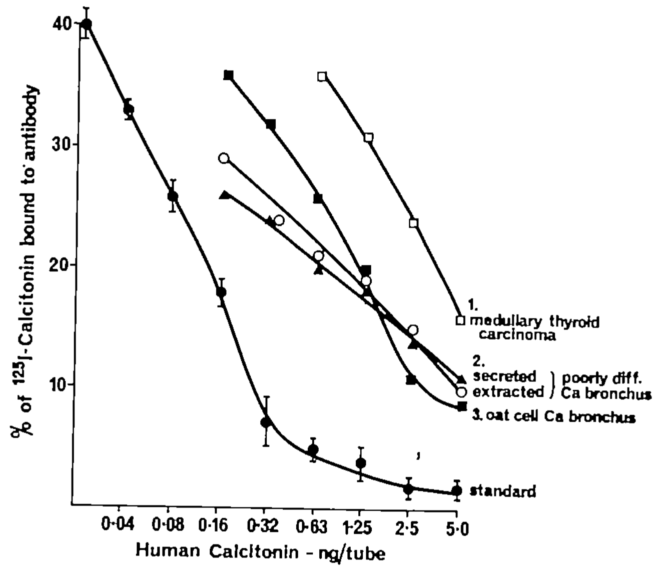

Fig. 4. Comparison of displacement of ^{125}I-calcitonin from antibody by calcitonin and by culture medium or extracts of various malignancies. The cell extract and culture medium of the poorly differentiated carcinoma are clearly immunologically distinct from the other materials

culture has been shown to be proportional to the volume of medium bathing the cells (Ellinson et al. 1976) and to the number of cells in a given volume of medium (to be published). It is also clear from these studies that the apparent circulating level of a tumour cell product need not bear a fixed relationship to the tumour cell mass, since feedback phenomena, difficulties in immunological quantitation and other, as yet undefined, factors tend to distort this relationship.

Concerning the role of the radio-immunoassay, as presently defined, in monitoring bronchogenic carcinoma, our series (Table II) indicates that high plasma calcitonin levels are found more commonly in 'oat-cell' carcinomas, as is the case for ACTH but not for oncofetal antigens such as carcinoembryonic antigen (CEA). Other groups have confirmed this observation (e.g. Tashjian et al. 1975) but the distinction is not absolute for one patient with a squamous cell bronchogenic carcinoma studied by us (Fig. 5) had elevated plasma levels of calcitonin and parathyroid hormone in both plasma and tumour tissue. In this patient, it can be seen that the rise in calcitonin level occurred with the clinically obvious recurrence in the chest wall at the site of thoracotomy.

Table II. Plasma calcitonin in bronchogenic carcinoma

Histology	*No. of patients*	*Plasma calcitonin* (µg/litre) <0.1	0.1–1	>1	*Total with raised levels*
Oat-cell	20	4	6	8	14/20
Squamous cell	11	9	1	1	2/11
Adenocarcinoma	1	1	0	0	0/1

Radio-immunoassay carried out by Dr C. J. Hillyard in the laboratory of Professor I. MacIntire.

Silva et al. (1976) have found hypercalcitoninaemia in 62% of 26 men with bronchogenic carcinoma and observed a decrease in hormone levels with successful therapy. They also demonstrated a thyroid origin for the high levels of calcitonin in one patient. Conceivably hypercalcitoninaemia in this individual could be secondary to release by the tumour of a calcitonin secretagogue, e.g. glucagon or gastrin.

It is clear that further studies are required to establish the precise place of the calcitonin radio-immunoassay in the management of patients with bronchogenic carcinoma.

Antidiuretic hormone. The syndrome of inappropriate antidiuresis most often occurs with oat-cell carcinomas; these patients are hyponatraemic and hypokalaemic, and concomitant measurement of plasma and urinary osmolalities can assist in monitoring the patients' response to therapy. Some studies have been carried out concerning the chemical nature of antidiuretic hormone (ADH) in tumours and chromatography indicates that some of the material elutes in a high molecular weight fraction (Rees 1975).

A recent study by Gilby et al. (1976) has shown that 34 of 49 unselected patients with oat-cell carcinoma had abnormal water load tests. In 17 of the 49 patients the syndrome of inappropriate antidiuretic hormone secretion was confirmed by observing elevated plasma ADH with hypotonic plasma and concentrated urine. In the remaining 17 of these patients the abnormal water load tests were thought to be due to the stress of the illness rather than ectopic secretion of ADH. Patients who responded to chemotherapy generally showed a return to normal of abnormal biochemical parameters.

Hypercalcaemia. Approximately 8% of patients with bronchogenic carcinoma will develop hypercalcaemia at some time in the course of their illness and the majority of these patients will be found to have squamous cell carcinoma (Azzopardi et al. 1970). Similarly, hypertrophic pulmonary osteoarthropathy is generally found only in association with tumours of this cell type, but only at an incidence of 2–4% (Yacoub 1965).

A proportion of patients with hypercalcaemia do not have detectable skeletal metastases and the serum calcium often falls following tumour resection (Fig. 5), suggesting that the tumour was capable of secreting a hypercalcaemic material. This is important since a factor such as this could be used to monitor progress in these patients, for it is likely to be more sensitive than measurement of the serum calcium alone.

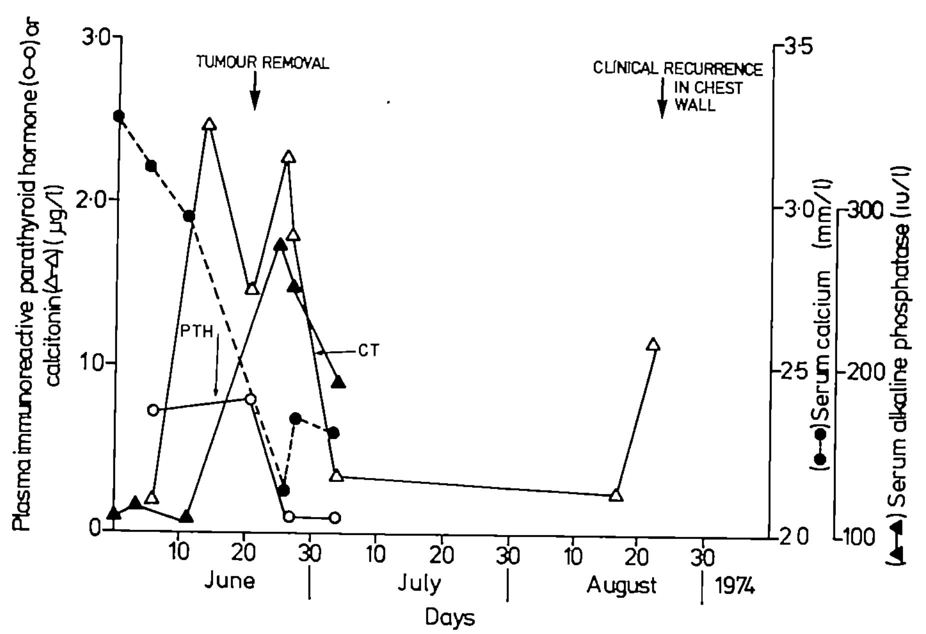

Fig. 5. Ectopic production of immunoreactive PTH and calcitonin in a patient with a squamous cell bronchogenic carcinoma. PTH levels (normal < 0.76 µg/litre) were high (for this serum calcium) preoperatively, as were calcitonin levels (normal < 0.1 µg/litre). Following removal of the primary tumour both these hormone levels fell, with a concomitant rise in alkaline phosphatase. Calcitonin rose at the time of clinical recurrence of tumour in the chest wall. The tumour contained significant amounts of immunoreactive PTH (6.44 µg/g tumour; 0.81 µg/g normal lung) and calcitonin (0.49 µg/g tumour; 0.016 µg/g normal lung)

The nature of the material responsible has eluded investigators for many years. The most likely candidate responsible is parathyroid hormone (PTH), but the evidence is still not conclusive, mainly due to lack of a sufficiently sensitive radio-immunoassay. Sherwood et al. (1967) were the first to find increased concentrations of immunoreactive PTH in squamous-cell bronchogenic carcinomas and these results were confirmed by Berson and Yalow (1968). Roof et al. (1971) demonstrated that tumour-associated PTH was immunologically distinct from 'native' hormone and the nature of this difference was partly elucidated by Benson et al. (1974) who identified three molecular weight forms of PTH in the plasma of patients with this syndrome. These were of larger molecular weight than the recently isolated precursors 'Pre-pro PTH' and 'Pro PTH' (Potts 1976), and were possibly protein-bound forms of the hormone.

It is becoming clear that few cases of hypercalcaemia complicating this tumour are likely to be due to elaboration of tumour PTH. Thus, serum calcium in some patients falls following the administration of prostaglandin synthetase inhibitors (see Fig. 6, Patients A, C), and this suggested that prostaglandin synthesis may be involved. The second line of investigation that we pursued was to study the metabolic abnormalities that occurred in association with this tumour (Table III) (Coombes et al. 1976*b*). The patients were unlike patients with hyperparathyroidism, where a high intestinal absorption of calcium, high bone turnover rate, an elevated PTH and cyclic AMP excretion are found. Instead, six of nine patients had reduced intestinal absorption of calcium and only the two patients with hypertrophic pulmonary osteoarthropathy had an elevated ^{47}Ca space (a measure of bone turnover rate). Further, plasma PTH was elevated in only one of eight patients and this patient had elevated cyclic AMP excretion (No. 2, Table III). The two patients without skeletal metastases did not differ from the other seven patients. The factor responsible for hypercalcaemia in these patients remains to be identified.

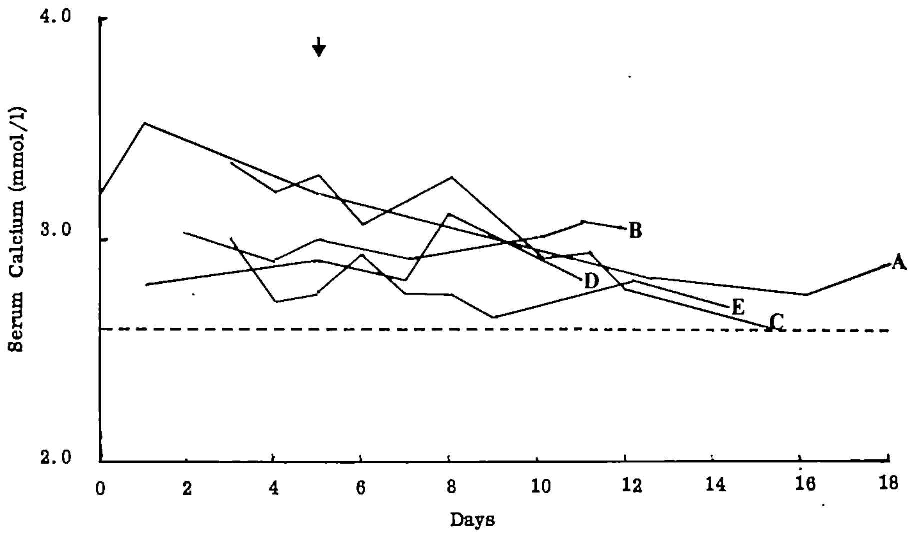

Fig. 6. Effect of indomethacin on serum calcium in hypercalcaemia complicating bronchogenic carcinoma. Indomethacin (300 μg/day) was given to five patients with squamous cell carcinoma and hypercalcaemia. Two patients (patients A, B) had skeletal metastases. Two patients (patients A, C) responded with a fall in serum calcium. This is unlike the effect in breast carcinoma in which none of six patients responded to similar doses of indomethacin

Table III. Calcium metabolism in bronchogenic carcinoma

Patient No	*Histology*	*Skeletal metastases*	*Serum calcium* (mmol/litre) (corrected)	*Calcium absorption* (% dose administered)	*24-hour ^{47}Ca space* (plasma units)	*Urinary calcium* (mmol/day)	*Plasma PTH* (μg/litre)	*Plasma calcitonin* (μg/litre)	*Urinary cyclic AMP* (mmol/day)
1	—	No	2.3	19±2	15.4	2.5	—	N.D.	—
2	Squamous cell	Yes	2.4	37±5	18.3	1.5	0.95	1.7	2.81
3	Anaplastic	Yes	2.5	25±2	16.0	2.2	0.24	—	—
4	Oat cell*	Yes	2.4	29±1	29.8	5.5	0.63	1.35	—
5	Squamous cell	Yes	3.0	32±3	15.6	4.5	0.23	N.D.	2.1
6	Squamous cell	Yes	3.35	24±3	13.1	24.7	0.53	N.D.	—
7	—	Yes	3.1	20±2	12.8	9.5	0.60	N.D.	1.93
8	—	Yes	3.4	23±2	10.9	4.2	0.32	N.D.	0.27
9	Squamous cell*	No	3.1	41±2	29.5	9.5	0.70	2.48	—
Normal range			2.4–2.6	30–58	10–18.2	1.8–4	<0.1–0.76	<0.1	1.37–2.57

* Hypertrophic pulmonary osteoarthropathy.

— = Not performed: N.D. = Not detectable. Data from Coombes et al. (1976*b*).

Table IV. Range of abnormality of potential markers in ten unselected patients with inoperable lung cancer, with no clinically evident distant metastases

Patient No.	*Tumour histology*	*Calcitonin*	*PTH*	*β-HCG*	*Insulin*	*FSH*	*GH*	*CEA*	*Alkaline phosphatase*
1	Oat cell	+	–	–	–	–	–	–	+
2	Oat cell	–	–	–	–	–	–	–	–
3	Oat cell	+	–	+	–	+	–	–	+
4	Oat cell	–	–	–	–	–	–	–	+
5	Squamous cell	–	–	–	–	–	–	–	+
6	Squamous cell	–	–	–	+	–	–	–	–
7	Adenocarcinoma	–	+	–	–	–	–	–	+
8	Adenocarcinoma	+	–	–	–	–	+	–	–
9	No histology	–	–	–	–	–	–	–	+
10	No histology	–	–	–	–	–	–	+	–

+ = elevated level; – = within normal range. PTH = parathyroid hormone; β-HCG = β-subunit of human chorionic gonadotrophin; FSH = follicle-stimulating hormone; GH = growth hormone; CEA = carcinoembryonic antigen. In this series, plasma glucagon, luteotrophic hormone, thyroid-stimulating hormone, prolactin and vasoactive-intestinal polypeptide were normal in all patients. Measurements were carried out by C. J. Hillyard, K. Mashiter and S. Bloom.

Placental hormones. Choriocarcinoma and ovarian and testicular teratomas contain tissue derived from trophoblastic sources and the production of human chorionic gonadotrophin is thus an appropriate function. Few, if any, pulmonary tumours contain trophoblastic elements but one human cell line derived from a bronchogenic carcinoma has been described that secretes the two subunits (α and β) of this hormone in vitro (Tashjian et al. 1973). Different clones of this cell line produce different proportions of the subunits and the amount secreted bears some relationship to cell number.

Rosen et al. (1968) found three of 106 patients with bronchogenic carcinoma to have high levels, and Braunstein et al (1973) found one of 15 with high levels, so the proportion of patients who can be usefully monitored utilizing the radio-immunoassay for HCG is relatively small and Hagen et al. (1976) have indicated that ectopic production of HCG rarely occurs in oat-cell bronchogenic carcinoma. Levels in 36 patients with this carcinoma were not found to differ significantly from those found in chronic renal failure. In view of the difficulty of obtaining truly specific antisera for the different glycoproteins and/or their subunits, some of the discrepancies noted above may be related to the reagent probes used.

Human placental lactogen (HPL), another placental hormone, has been found to be elevated in some patients with bronchogenic carcinoma (Weintraub & Rosen 1971).

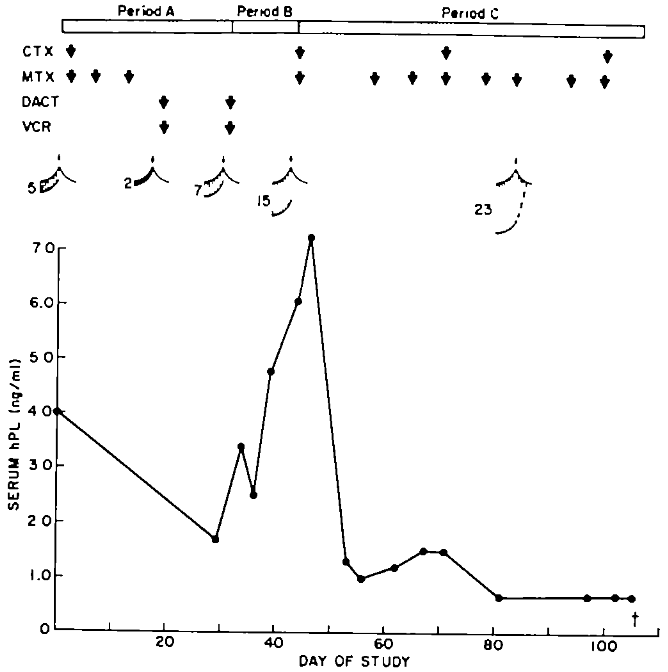

Fig. 7. Serial measurements of serum HPL concentrations with changes in liver size at therapy (stippled bar) or no therapy (clear bar) periods. CTX = cyclophosphamide; MTX = methotrexate, DACT = dactinomycin, VCR = vincristine. (*From Muggia et al. 1975*)

These workers detected this peptide in extracts of two bronchogenic tumours associated with gynaecomastia. High circulating concentrations of HPL were found in these patients and an example of the use of sequential HPL measurements is shown in Fig. 7.

Multiple hormones. Mention has already been made of concomitant ACTH and calcitonin production and of the association of PTH and calcitonin production. Other recognized combinations are ACTH with MSH or ADH with oxytocin (Rees & Ratcliffe 1974). A single bronchial tumour, described by Rees et al. (1974), was capable of secreting ACTH, ADH, oxytocin, neurophysin, insulin, prolactin and corticotrophin-like intermediate-lobe peptide.

It is clear that abnormalities of hormone levels are commonly found in patients with bronchogenic carcinoma, and this raises the possibility of measuring several parameters in a single patient, as has been suggested for breast carcinoma (Tormey et al. 1975; Coombes et al. 1977).

We have evaluated 11 hormones in the plasma of 10 unselected patients with bronchogenic carcinoma (Table IV), and found that six of ten patients had abnormally high levels of at least one hormone, indicating that a study of a larger series may be warranted to assess the value of measuring several hormones in the management of these patients. CEA and alkaline phosphatase also seem useful in a multiparametric appraisal.

Oncofetal antigens

In man and experimental animals, antigens have been characterized that are expressed as a major product by both fetal and neopastic tissues. The so-called carcinoembryonic antigen (CEA) of Gold and Freedman (1965) and alpha-fetoprotein (AFP) are the major examples.

Carcinoembryonic antigen (CEA). This is a glycoprotein with a molecular weight of approximately 200 000. Originally thought to be specific for fetal and neopastic gastrointestinal tissue, it has subsequently been found in association with many different neoplasms. Although CEA does not appear to be present in fetal lung (Lo Gerfo et al. 1972) it is found in lung tissue of patients dying with non-malignant disease.

Evaluation of this product in bronchogenic carcinoma is complicated by the fact that many patients with non-neoplastic lung disease have high levels (Table V); further, heavy smokers have elevated plasma levels and these factors tend to obscure the value of the CEA radio-immunoassay. Unfortunately, CEA in bronchial tumours does not

Table V. Number of patients with various conditions, related to their plasma CEA level

Disorders	*Plasma CEA level* (ng/ml) <12·5	<20	<40	>40
Normal	60	–	–	–
Carcinoma of bronchus	11	16	4	6
Pulmonary tuberculosis	13	5	3	—
Chronic bronchitis/cor pulmonale	10	6	4	1

From Lawrence et al. 1972.

appear to be chemically distinct from the material found in other tumours, and development of more specific radio-immunoassays is unlikely.

Laurence et al. (1972) (Table V) found 26 of 37 patients with bronchial carcinoma to have high levels; the levels were unrelated to tumour histology, but were related to stage.

A large group of patients was presented by Vincent et al. (1975), and indicated that an elevated preoperative value of CEA was likely to indicate the presence of metastases (Fig. 8). Thus, in an assay in which the upper limit of normal was 2.5 μg/litre, 49 of 228 patients had a level in excess of 15 μg/litre and 42 of those 49 had metastatic disease. In 47 patients considered suitable for resection of the primary tumour, the mean CEA was 4 μg/litre. Within 2.5 years of follow-up, 23 cases developed overt metastases. In those

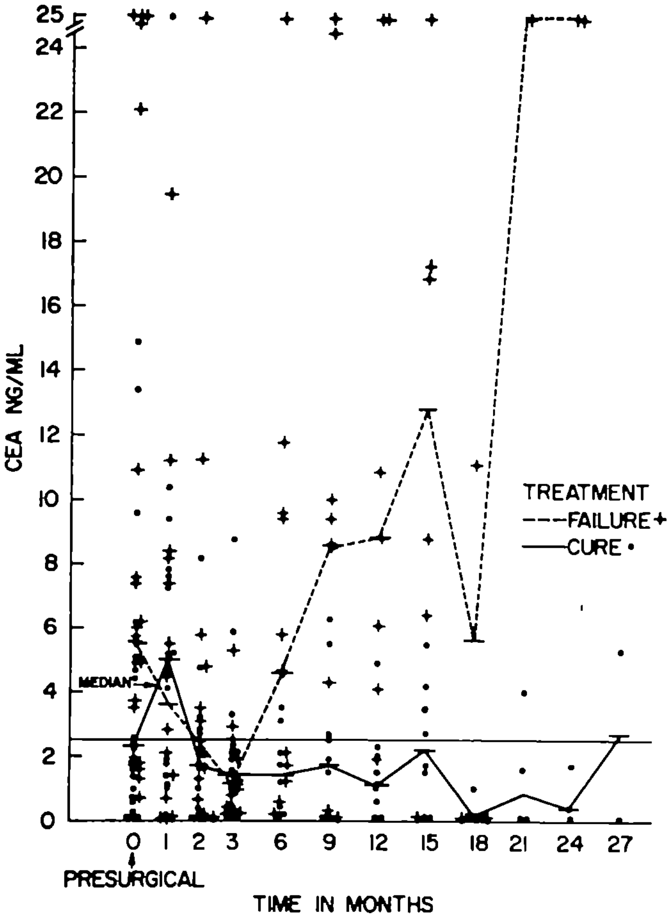

Fig. 8. The postoperative values of CEA in those patients in whom surgical treatment ultimately failed are compared with those interval CEA values of patients who were thought to be cured by a pulmonary resection. Among those patients in whom treatment eventually failed there is a very significant increase in CEA values which begins at the sixth postoperative month but is sustained until the death of the patient. (*From Vincent et al. 1975*)

whose disease remained localized eight of 24 had high levels preoperatively, and in those who developed metastases 14 of 23 had high levels. It is not possible to calculate the 'lead-in time' (the length of time that the CEA value was elevated before the development of overt metastases) from these data, but in 13 patients who died in whom the CEA levels were elevated on one or more occasion postoperatively, the average time that the CEA was elevated consistently before death was about 6 weeks (Fig. 8).

A more recent study (Ford et al. 1977) indicated that the radio-immunoassay is useful for only a small proportion of patients. Only 6% of patients had CEA levels in the diagnostic range (> 50 μg/litre) at the time of presentation. These workers found no difference in CEA levels between those who had mediastinal lymph node involvement at operation and those who did not. Sequential estimations showed that the CEA reflected the disease status either at the same time or before evidence of secondaries in only seven of 22 patients The 'lead-in time' varied between 3 and 8 months. No satisfactory study has been published concerning its use in following patients with overt metastatic disease since the value of staging and the roles of chemotherapy and radiotherapy in this disease are only currently being defined.

The quantitative aspects of CEA output by a human lung carcinoma cell line in vitro

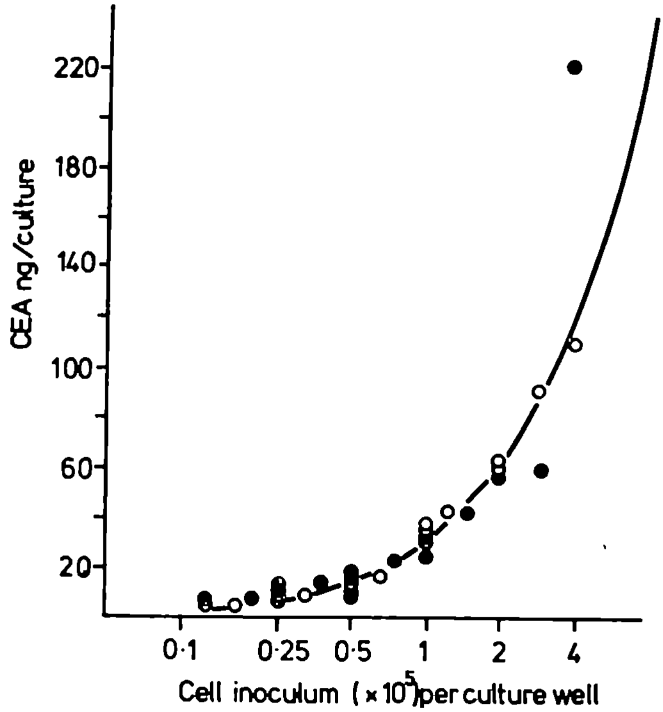

Fig. 9. CEA production relative to the number of bronchial carcinoma cells in vitro. Passage 52, 3+2 days' preincubation (●); passage 79, 3 days' preincubation (○). CEA was measured in 1 ml medium/culture for the final 24 hours after the preincubation period. The solid line illustrates the theoretical relationship between cell number and CEA output if one assumes direct proportionality. (*From Ellison et al. 1977*)

have been studied by Ellison et al. (1977). They found that although CEA output was proportional to the number of cells, under controlled conditions (Fig. 9) the output varied with the type of culture medium. With this difference in CEA output per cell, the output of CEA was inversely related to the growth rate. Also a sudden release of CEA was observed when the cells were killed by exposure to a high pH or lethal temperature (Fig. 10). Thus, the amount of marker released and detected cannot be used as a direct indication of tumour bulk.

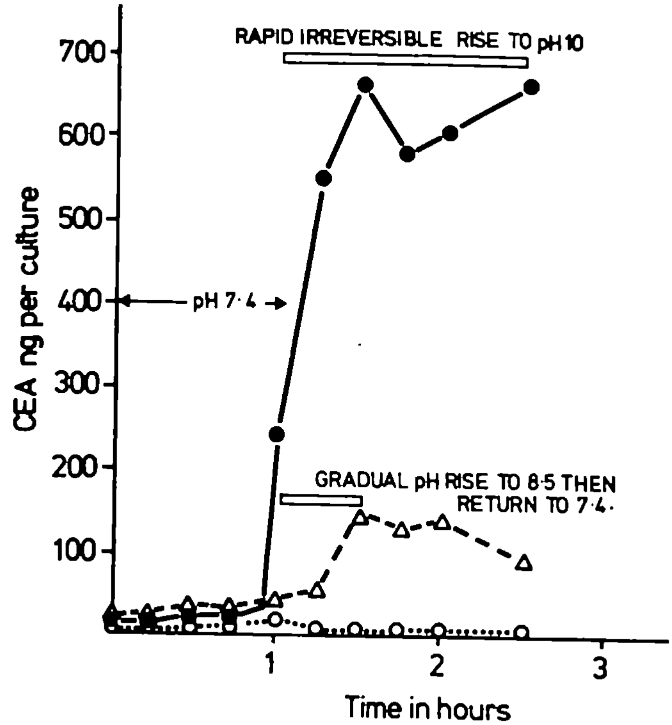

Fig. 10. Cell death and CEA secretion. Cells of passage 64 plated at 0.1×10^6 cells/well in 1 ml growth medium. (*From Ellison et al. 1977*)

Other oncofetal antigens. Alpha-fetoprotein (AFP) was found to be elevated in only a minority of patients with bronchogenic carcinoma. Thus, of a recent series of 30 patients, only a single patient had a level of AFP in excess of the normal range. In this same group of patients, 13 of 30 had elevated levels of CEA (Grigor et al. 1976). Whether the AFP in bronchogenic carcinoma derives from the tumour is not certain since a recent report, utilizing immunofluorescence, indicated that the liver was the site of production (Tsung 1975).

In 1975, Fritshé and Mach described a β-oncofetal antigen (β-OFA) and isolated it in approximately similar concentrations from both fetal and malignant lung tissue. Earlier, Edynak et al. (1972) described a fetal antigen termed γ-fetoprotein and found this in five of 13 bronchogenic tumours but not in normal lung and benign lung disease. However they could not detect the materials in the plasma of patients with bronchogenic carcinoma.

Ferritin, the iron-binding protein, has recently achieved a role as a tumour index substance, and was originally described in this context as an α_1H fetoprotein by Buffe et al. (1973).

Its value in the management and diagnosis of leukaemia has recently been documented (Worwood et al. 1974) and it has been extensively investigated in breast carcinoma (Marcus & Zinberg 1975), but its role in bronchogenic carcinoma has not been adequately studied. However elevated values have been found in a few patients with a variety of types of bronchogenic carcinoma (Niitsu et al. 1975).

Enzymes

In 1968, Fishman et al. isolated a placental alkaline phosphatase from a bronchogenic carcinoma. Subsequently seven of 51 patients with bronchogenic carcinoma were found to have this form of alkaline phosphatase circulating. The study of Jacoby and Bagshawe (1972), however, failed to confirm this proposition. No good data demonstrating the use of this isozyme in a longitudinal study have been published.

Many subtle changes occur on malignant cell membranes when compared with normal cells and components forming part of the cell surface can be quantitated in patients with neoplasms. Major structural alterations of the cell surface glycoprotein occur and, in addition to this, increases in sialic acid content on the cell surface are found in malignant tissues. Levels of enzyme activity involved in the transfer of sialic acid residues to acceptors are elevated in malignant cells. Thus, plasma 'sialyl transferase' levels have been measured in malignancy (Kessel & Allen 1975). In this report two of four patients with bronchogenic carcinoma had elevated levels.

Galactosyl transferase activity is also increased in the serum of patients with tumours, and there appears to exist a different form of galactosyl transferase (galactosyl transferase isoenzyme II) in tumour-bearing patients. Seven of eight patients with bronchogenic carcinoma had this isozyme circulating, the level appearing greater in those with widespread metastases (Weiser et al. 1976).

Measuring enzymes of this nature could assist in monitoring disease activity since they presumably constitute a further variable to add to a multiparametric assessment.

Cell-turnover products

Recent advances in separation of chemical materials has resulted in the identification of many products of cellular metabolism and turnover that had not previously been identified. The polyamines are widely distributed aliphatic materials present in all nucleated cells and increased tissue polyamine levels correlate well with rises in protein synthesis. Russell documented the occurrence of high levels of polyamines in the urine of patients with bronchogenic and other carcinomas in 1971. Since this time others (e.g. Dreyfuss et al. 1974) have found high levels in non-neoplastic conditions.

There are four polyamines, putrescine, spermidine, spermine and cadaverine, each separable by chromatography. Russell has recently advocated the use of polyamine determinations as an indicator of response to therapy since the rise of polyamine excretion produced by chemotherapy correlates with the ultimate response to treatment (Russell et al. 1975).

Patients with metastatic bronchogenic carcinomas excrete large quantities of these materials (Lipton et al. 1975) (Fig. 10). These results were confirmed by Waalkes et al. (1975*a*) who found putrescine, spermine and spermidine elevated in 54% (42 of 83), 34% (28 of 82) and 50% (41 of 82) of patients respectively. As with CEA, the degree of elevation did not appear to bear any relationship to the histology of the primary tumour nor to the site of the metastases. Higher levels are found in patients with metastases.

The methylated nucleosides and pseudouridine are breakdown products of transfer and microsomal RNA, and several studies have indicated their occurrence in the urine and plasma of patients with tumours (Adam et al. 1960; Levine et al. 1975; Waalkes et al. 1975*b*).

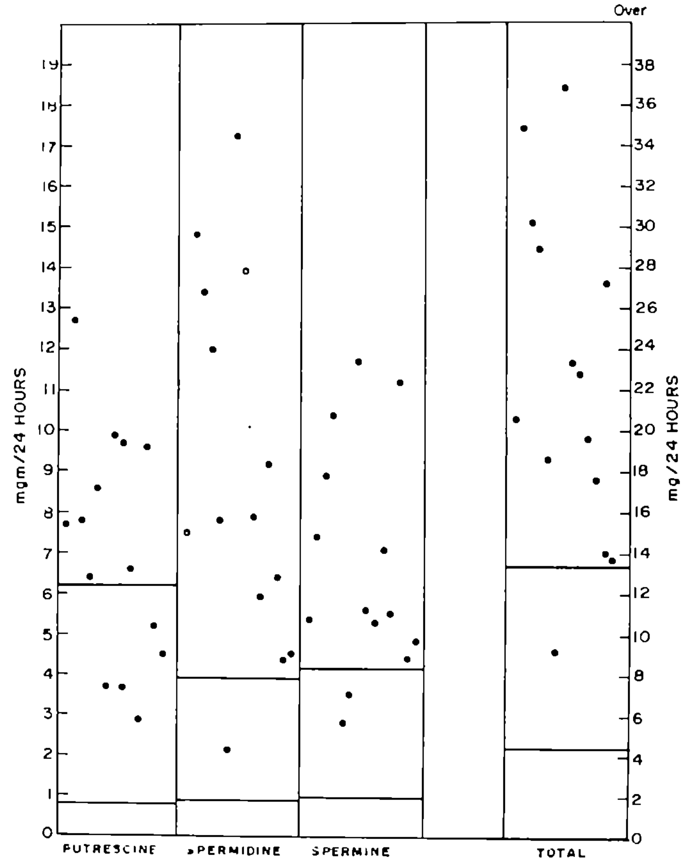

Fig. 11. Urinary polyamine excretion in bronchogenic carcinoma. (*From Lipton et al. 1974*)

Chang et al. (1974) using gas–liquid chromatography, studied 67 patients with bronchogenic carcinomas and found that 69% had elevated levels of urinary dimethylguanosine; methylinosine and pseudouridine levels were elevated in 60% and 34% respectively. Studies have yet to be published detailing the value of nucleoside measurements in assessing response to therapy although nucleoside excretion in Burkitt's lymphoma appears to bear some relationship to response (Waalkes et al. 1975*c*).

TUMOUR-ASSOCIATED CHANGES

Glycoproteins, globulins and acute-phase proteins

It has long been recognized that many changes occur in the serum proteins of patients with cancer, although the reason for these changes is unknown. The consensus of current opinion is that such changes play little or no part in facilitating the earlier detection of localized tumours or in their differential diagnosis (Neville & Cooper 1976).

The most valuable parameter in this class of markers appears to be β_2-microglobulin, reported initially by Evrin and Wibell (1973) and evaluated more extensively by Shuster et al. (1976) who found elevated levels in 26 of 78 patients with bronchogenic carcinoma. These workers found the highest levels in patients with bronchogenic neoplasms, whilst patients with Hodgkin's disease and lymphoma had relatively low levels. Levels are, however, elevated in patients with renal impairment (Evrin & Wibell 1973) and other inflammatory diseases (Kithier et al. 1974).

Recently, pregnancy-associated macroglobulin (PAM) has been found to circulate in increased amounts in patients with cancer (Stimson & Sinclair 1974). They have found elevated PAM concentration in six of 14 patients with metastatic bronchogenic carcinoma although those with localized disease had normal levels (Stimson 1975).

An abnormal glycoprotein has been isolated from the urine of a patient with acute myeloblastic leukaemia and a radio-immunoassay for this glycoprotein (EDC one) was developed. A patient with oat-cell bronchogenic carcinoma was monitored and the level in the urine fell from 250 ± 39 ng/ml to below 200 ng/ml on attaining remission with chemotherapy (Rudmann et al. 1977).

Hydroxyproline excretion

Bone scanning has helped considerably in the detection of skeletal metastases but even this is a relatively insensitive tool in the detection of small amounts of skeletal destruction.

Calcium excretion is an inaccurate guide due to the changes that occur with dietary calcium and altered renal function and therefore hydroxyproline excretion, frequently measured to monitor other bone diseases (e.g. Paget's disease), has been evaluated in patients with osteolytic destruction by metastatic carcinoma.

Guzzo et al. (1969) found that all of five patients with bronchogenic carcinoma and overt skeletal metastases had elevated levels of hydroxyproline and 12 of 17 patients with apparently localized bronchogenic carcinoma had values in excess of controls.

Recent studies at our institute have disclosed much lower excretion values for those patients without overt metastases both for bronchogenic (P. K. Bondy, personal communication) and breast (Coombes et al. 1977) carcinomas.

No study has yet demonstrated the superiority of hydroxyproline excretion over technetium bone scanning in detecting skeletal metastases in bronchogenic carcinoma.

Liver-related enzymes

These are of obvious importance in monitoring patients with malignancies. The tumour causes release of enzymes from normal hepatocytes as they are destroyed by the invading cells, or enzymes are released secondarily to obstruction of bile ducts. In addition the tumour can occasionally promote the release of enzymes from liver tissue not directly involved by tumour.

It has been suggested (Neville & Cooper 1976) that the evolutuon of hepatic metastases can be divided biochemically into a number of stages. The first stage is said to be completely silent, but subsequently a slow rise of gamma glutamyl transpeptidase (GGT) occurs after or coincident with a rise in CEA in colorectal carcinoma. Following this the rate of rise of GGT increases and at this stage the 5-nucleosidase, alkaline phosphatase and the serum transaminase activities increase.

It is clear therfore that the usual biochemical tests for hepatic metastases reflect disease at a relatively late stage in its development. There is some suggestion that liver disease can exaggerate the increase in levels of CEA by altering its metabolism (Thomas et al., unpublished). Ferritin levels also rise following hepatocellular damage (Marcus & Zinberg 1975).

LUNG TUMOUR ANTIGENS

Much work has been carried out concerning the antigenic determinants of human bronchogenic carcinoma and this forms the basis of a recent review (Price Evans 1976). Bell has raised antisera to bronchogenic adenocarcinoma cells and following absorption with normal human plasma found antigenically similar material in all extracts of adenocarcinomas, but also in extracts of normal peripheral lung tissue (Bell 1976).

McIntire et al. (1977) have reported an antigen in 78 of 90 primary bronchogenic carcinomas but were unable to identify this reaction with normal lung samples.

The growth of lung tumours in experimental animals has permitted xenogenic serum to be analysed and antisera with reactivity against lung-tumour-derived cell lines have been raised. 11 of 24 patients with lung carcinomas and two of 15 patients with other tumours had a circulating 'antigen' binding to this antiserum (Kempner 1977).

CONCLUSIONS AND FUTURE APPROACHES

It is clear from this review that no adequate single tumour index substance, akin to those in use for some endocrine tumours, exists for this tumour at present. A few tumour index substances fulfil one or other role of an ideal marker, but assessment is often difficult due to lack of clearly defined histological subgroups or inadequate staging. Bearing these factors in mind, some tentative conclusions can be made.

None of the biochemical parameters have been tested for efficacy in primary detection of bronchogenic carcinoma. Current screening programmes (e.g. Melamed et al. 1977) utilize chest radiography and sputum cytology for detecting early peripheral adenocarcinomas and epidermoid carcinomas of major bronchi respectively. None of the present biochemical tests is likely to be sufficiently sensitive for primary detection. Undifferentiated bronchogenic carcinomas (small-cell or oat-cell variety) are likely to be disseminated at the time of detection by either radiological or cytological techniques.

Estimation of plasma calcitonin, ACTH or ADH may prove of value in the differential diagnosis of a radiographic opacity when it is not possible to obtain material for histological examination. Any abnormality of these three hormone products is likely to indicate the presence of an oat-cell/small-cell tumour. Conversely, hypercalcaemia is usually associated with squamous-cell carcinomas. Abnormalities of most of the other products do not appear to distinguish tumour tupe.

Having established the diagnosis, biochemical tests can give some idea as to the presence of metastases. Thus, a high plasma ACTH (Yalow et al. 1977), CEA (Laurence et al. 1972), or excretion of polyamines (Lipton et al. 1975) indicates spread of tumour, as do abnormal liver-related enzymes or hydroxyproline excretion (Guzzo et al. 1969).

In operable tumours, serial estimations of any or all of these parameters could assist in detecting recurrence and most have yet to be evaluated. A role for some in monitoring metastatic disease is suggested by several studies. Thus, calcitonin, ACTH, HCG, HPL, CEA, ferritin, placental alkaline phosphatase, the polyamines and some of the acute-phase proteins have all been serially measured in this disease and found to parallel disease activity. Perhaps specific immunoperoxidase localization of a product in primary tumour tissue could help define the substances secreted by a tumour; this would provide a more logical basis for sequential measurement of any particular product.

As we have suggested in the case of breast cancer (Coombes & Neville 1977), it is unlikely that a single marker will suffice to monitor this tumour: a multiparametric approach will be needed, with measurement of several independent variables. Studies of this sort should be accompanied by parallel radiographic and other physical measurements.

Although many of the markers outlined above have yet to be fully evaluated, it is likely that future advances in this field will come from a more fundamental approach. Recent work has indicated that the lung is a complex functioning endocrine organ and Feyrter (1954) described a group of 'clear cells' in the bronchial epithelium of many mammals, whch are now believed to contain and secrete amines, peptides and prostaglandins and have APUD (amine-precursor-uptake-decarboxylation) characteristics (Pearse 1969). These secretions could influence primary vasoconstriction response, and their activity appears to increase with the degree of hypoxia in mammals (Lauweryns & Cokelaere 1973). They therfore seem capable of responding to the environment and the effect of the carcinogens present in tobacco smoke on the metabolism of these cells requires urgent investigation.

The preliminary tissue culture studies described here (Ellison et al. 1976, 1977) indicate that lung tumours are complex functioning systems with feedback control and regulation and underline the need for further studies whose relevance could have important clinical ramifications.

The chemical studies concerning the nature of lung tumour products (e.g. calcitonin, ACTH) indicate that differences occur in the pattern of molecules secreted. Thus, more specific antisera can be raised to these products resulting in improved methods of immunological detection.

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PULMONARY AND PLEURAL LESIONS IN RHEUMATOID DISEASE

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Summary

Lung and pleural involvement in rheumatoid disease is reviewed and discussed. Attention is drawn to the male preponderance, to the frequency with which lung infections occur in rheumatoid patients and to some problems posed in them by infection with mycobacteria. Pleural effusion, pulmonary nodules and fibrosing alveolitis are familiar in association with rheumatoid arthritis. Less familiar associations include upper lobe fibrosis, 'shrinking lung' and mixed pleural and pulmonary involvement. It is suggested that rheumatoid patients display a wider range of intrathoracic disease than seems generally appreciated.

INTRODUCTION

The common and widespread nature of systemic features of rheumatoid arthritis justifies the term rheumatoid disease. When a disease is common it is often difficult to be sure that an association is causal and this has hindered recognition of the association of pulmonary disorders due to rheumatoid disease. Four thoracic complications are generally accepted as part of rheumatoid disease: pleural effusion (Walker & Wright 1967), fibrosing alveolitis (Scadding 1969), pulmonary nodules (Rubin et al. 1967) and Caplan's syndrome (Caplan et al. 1962). Other lesions reported include acute pulmonary changes (Beck & Hoffbrand 1966), dry pleurisy (Short et al. 1957), pleural thickening (Gardner 1972), empyema (Dieppe 1975*a*) and pulmonary vascular changes (Ellman & Ball 1948). Many of these lesions may occur before the appearance of joint manifestations, and combinations of lesions have been discribed (Scadding 1969).

The authors have had the opportunity study a number of patients at Guy's, St Bartholomew's, Brompton and the Brighton hospitals. In addition to the lesions mentioned above a number of unusual lesions have been identified. This report reviews the literature, describes some of the variants and draws attention to the variety and extent of the pulmonary complications of rheumatoid arthritis. These are considered under the broad headings of pleural and pulmonary involvement, with a preliminary section on infection—perhaps the commonest respiratory problem in rheumatoid arthritis.

INFECTIONS

Bronchitis and bronchiectasis are commoner in patients with rheumatoid arthritis coming to autopsy than in matched controls (Aronoff et al. 1955). Illnesses diagnosed as chronic bronchitis and pneumonia were more frequent in men with rheumatoid arthritis than in those with degenerative joint disease (Walker 1967), but radiological evidence of previous pulmonary tuberculosis was equally common. However, other reviews report that tuberculosis was commoner in rheumatoid patients (Baum 1971; Cobb & Hall 1965; Miall 1955). Cobb et al. (1953) reviewed several published series and report a range of 5–11% for the proportion of deaths in rheumatoid arthritis attributed to tuberculous infection.

Tuberculosis may be a diagnostic problem, especially in the differential diagnosis of a solitary pulmonary nodule (see Case 6, for example). We have in addition seen an ex-miner with pneumoconiosis develop a single shadow and produce an atypical mycobacterium:

Case 1. An engineering and survey assistant aged 52 years developed rheumatoid arthritis in 1969. He had worked in coal mines for 3 years before the Second World War and had normal chest radiographs in 1946 and 1950. In 1952 fine reticulation was seen in his chest radiograph. There was no history of respiratory illness and no symptoms. He was followed up regularly and had negative sputum cultures and no progression in the radiographic appearances. In 1962 he became ill and a confluent shadow appeared in the left upper zone. A single isolation of an atypical anonymous *Mycobacterium* (psychrophilic non-chromogen) was confirmed by the Tuberculosis Reference Laboratory in Cardiff. This organism rarely acts as a pathogen, except in people with pneumoconiosis. When seropositive, erosive arthritis developed in 1969, corticosteroid therapy was strictly proscribed because of the risk of an overt atypical mycobacterial infection. Except for a transient pleural effusion in 1972 the chest radiographs have shown no change in the pneumoconiosis or in the left upper zone shadowing.

Corticosteroids should be withheld from all patients with a history of pulmonary tuberculosis, or prophylactic cover should be given, as the next case illustrates.

Case 2. A housewife aged 49 years, developed rheumatoid arthritis in 1961. Nineteen years earlier she had been ill with tuberculosis and had spent 18 months in a sanatorium. In 1963 corticosteroids were given for arthritis, and she became seriously ill in 1966 with a recrudescence of her pulmonary tuberculosis. This was confirmed by sputum culture.

Corticosteroid therapy was possibly a contributory factor in the next case where bronchiolitis proved fatal.

Case 3. A housewife aged 56 years had five years of seropositive, erosive, anodular rheumatoid arthritis and nine months of dyspnoea on effort before her last admission with severe shortness of breath. She had no cough, chest pain or purulent sputum and no evidence of cardiac failure. The dominant physical sign was of a diffuse high-pitched wheeze with no other adventitious sounds. Repeated chest radiographs showed normal lung fields. Despite increased corticosteroids and antibiotic therapy, progressive deterioration ensued and she died on the seventeenth day. Autopsy showed some areas of emphysema and collapse and histology showed acute bronchiolitis with a few areas of hyaline membrane. There was no evidence of any fibrosing alveolitis.

Acute bronchiolitis is a diagnosis not usually contemplated outside infancy. Whether corticosteroids or rheumatoid disease predispose to a viral infection is uncertain. There was no evidence of any bacterial infection pre- or post-mortem.

Focal acute bronchiolitis was part of the histological appearances in the rheumatoid patients described by Cruickshank (1959) and Price and Skelton (1956). Four patients similar to ours have recently been reported by Geddes et al. (1977). All had progressive respiratory failure with essentially normal chest radiographs. None was reportedly receiving corticosteroids. Post-mortems were obtained in three and the histological appearance was obliterative bronchiolitis.

Fungal infections in rheumatoid patients are apparently rare. We have seen a 52-year-old woman with rheumatoid arthritis and a history of pulmonary tuberculosis who developed an invasive pneumonia and an *Aspergillus niger* mycetoma without any other predisposing factors, in particular no corticosteroids.

PLEURAL CHANGES

Post-mortem studies (Baggenstoss & Rosenberg 1943; Fingerman & Andrus 1943; Aronoff et al. 1955; Gardner 1972) suggest that pleural adhesions and disease are common in rheumatoid arthritis. The only evidence for pleural involvement may be a pleural rub (Short et al. 1957). In our experience this is an early feature of the disease:

> *Case 4*. An insurance clerk aged 41 years was admitted for investigation of a seropositive polyarthritis of 2 months' duration. There was no history of respiratory illnesses and no respiratory complaints. A pleural rub was heard on several occasions but there was no clinical or radiological evidence of effusions or other lung changes. The rubs disappeared when his joint disease was brought under control. He subsequently developed skin nodules and joint erosions but has had no further intrathoracic events.

Rubs have been described in children with juvenile rheumatoid arthritis (Romicka & Maldyk 1975) and, in our experience, at the onset of classical Still's disease.

A history of pleurisy in the 5 years after the onset of joint disease is more common in men with rheumatoid than in matched controls with degenerative joint disease (Walker & Wright 1967). A review of respiratory illnesses in 230 women with rheumatoid arthritis and matched controls showed a higher incidence (20:6) of pneumonia and pleurisy in the rheumatoid group. Of the 20 patients, 17 reported that their respiratory illness preceded the arthritis (Kay 1967).

Small effusions are perhaps the commonest pleural association, and may be only an incidental radiological finding. Large effusions may recur after aspiration and may be very slow to resolve.

The pleural fluid may exhibit a number of unusual features including low glucose concentration (Dodson & Hollingsworth 1966), low complement levels (Hunder et al. 1972), high lactic dehydrogenase concentration (Berger & Seckler 1966) and a high titre of rheumatoid factor (Walker & Wright 1967). None of these is diagnostic of rheumatoid disease as they have been described in the effusions of pneumonia, tuberculosis and carcinoma (Levine et al. 1968; Lillington et al. 1971). Though the identification of specific cells characteristic of rheumatoid pleural effusions has been suggested as a means of differential diagnosis (Spriggs 1973) we have found it difficult to identify the cell types accurately.

Pleural effusions may contain such a high white cell count as to look purulent. The association of empyema and rheumatoid disease has been reviewed by Jones and Blodgett (1971) and Dieppe (1975*a*). It has been suggested that empyemas might form from necrosis of rheumatoid nodules causing a pyopneumothorax, from infection of an effusion and from rheumatoid disease alone causing a massive exudation of leucocytes and fibrinoid débris into the non-infected pleural space (Dieppe 1975*b*).

Pleural shadowing on radiographs is often described but it is difficult to be certain that it is not intrapulmonary.

Faurshou (1974) has used fibrescopic thoracoscopy in three rheumatoid patients with pleuritis and claims that the parietal pleura was distinctive with slight diffuse inflammation, little thickening and multiple scattered vesicles or nodules giving a gritty 'frozen' surface. In all patients the visceral pleura was abnormal and different with macroscopic excrescences, blebs and fibrin but the histology was non-specific in two. The third patient showed a pleural nodule of typical rheumatoid characteristics as has been reported by Berger and Seckler (1966) and Lillington et al. (1971). The non-specific changes so often reported may be the result of infection.

PULMONARY CHANGES

Nodules and cavities

A solitary lung nodule may be rheumatoid, tuberculous or neoplastic and the lesion may appear long before the onset of arthritis.

Case 5. A shipping manager and a smoker with long-standing chronic bronchitis presented in 1966 at the age of 43 years, with haemoptysis and a worsening cough. A chest radiograph showed a right mid-zone opacity which cleared during 3 months' observation. In 1968 he had a further haemoptysis and X-ray showed opacities in the right middle and lower zones. No neoplastic cells or acid-fast bacilli were found in the sputum and skin tests for moulds were negative. There was no change in the chest radiographic appearances after 1 year on anti-tuberculosis treatment, though some partial regression of the mid-zone shadow occurred later. The right lower zone shadow has persisted since. In 1974 he developed seronegative, erosive rheumatoid arthritis and in 1975 a nodule on the left elbow. X-ray screening now shows a well-defined round opacity closely related to the pleura and with a little calcium in it.

A similar case has been reported by Turner-Warwick (1974) who mentions other patients with necrobiotic pulmonary nodules and no evidence of arthritis. Seven further patients with typical rheumatoid nodule histology have recently been described by Eraut et al. (1978). Two later developed rheumatoid arthritis but four, at an interval of 4–26 years, have not and remain seronegative for rheumatoid factor.

In the patient with established rheumatoid arthritis the appearance of a nodule still presents a problem. The fact that the lesion may cavitate does not make diagnosis any easier. Our next case underlines this aspect.

Case 6. A housewife and smoker aged 51 years had had seropositive, erosive rheumatoid arthritis for 6 years when she presented with a history of 6 months' malaise, night sweats and 9 kg weight loss. Respiratory symptoms were denied. The chest radiographs and tomography revealed a cavity in the right lower zone which had not been present 2 years earlier. Bronchial washings grew no tubercle bacilli. Mantoux test was positive. Thoractomy and subsegmental resection produced a histological specimen with areas showing giant cell granulomas containing acid-fast bacilli, and other sites with central fibrinoid necrosis surrounded by palisading fibroblasts and chronic inflammatory infiltration. The diagnosis of both tuberculosis and a rheumatoid pulmonary nodule would appear adequately supported.

A similar cavitating lesion associated with hemoptysis is described by Locke (1963). Cavitation in rheumatoid pulmonary nodules without evidence of infection or malignancy has been well documented by Sieniewicz et al. (1962), Noonan et al. (1963), Yates (1963), Hindle and Yates (1965), Contin and Oka (1966), Ramirez-R (1966), Portner and Gracie (1966) and Stengel et al. (1966). Nodules have also been reported to rupture through the pleura and produce a pneumothorax (Basten er al. 1966) or a pyopneumothorax (Hindle and Yates 1965; Davies 1966).

When the nodules are multiple diagnosis is no easier. The following case is of particular interest because, to our knowledge, it is the first reported association of lung disease and palindromic rheumatism:

Case 7. A woman now aged 47 years has had short-lasting intermittent attacks of joint pain, swelling and stiffness for 10 years. These usually last for only 3 days and she is symptom-free between attacks. All investigations were unhelpful and her latex test was negative then. In 1967 she had several blackouts which led to a diagnosis of epilepsy. More recently an abnormal focus in the temporal lobe has been found by EEG studies. A chest radiograph in 1968 showed multiple coin lesions for the first time. A biopsy of one of these in 1971 showed a necrotic, partly calcified centre with surrounding lymph follicles. No histological diagnosis was made but healed tuberculosis and rheumatoid nodule were considered. Since 1971 she has suffered attacks of tenosynovitis as well as of her more usual articular swelling. She has since produced a raised ESR, a 1:64 differential agglutination titre and a lump related to tendons at the dorsum of the wrist which has the histological characteristics of a rheumatoid nodule. She is dyspnoeic on exertion and respiratory function tests show that her pulmonary gas transfer is only 40% of the predicted value. The multiple nodular lesions persist.

Vascular changes

Vasculitis occurs in a number of sites in rheumatoid disease and could appear in the lung and produce transient radiographic shadowing.

Case 8. A market gardener aged 52 years suffered an explosive onset of rheumatoid arthritis in 1970 with fever, malaise and weight loss in addition to polyarthritis. Nodules, and later vasculitis, were found. A chest radiograph showed pleural effusion and a pulmonary shadow which disappeared on corticosteroids when previous antibiotic therapy had failed.

A similar presumed non-infectious transient infiltrate, reversed by corticosteroids, has been noted by Beck and Hoffbrand (1966). Lung biopsy proof of any acute vasculitis is lacking.

Tomasi et al. (1962) suggested that immune complex deposition in pulmonary vessels might occur but there is little direct evidence for this. Immunofluorescent studies on lung biopsies from rheumatoid patients have shown IgM deposition in pulmonary arterioles and alveolar walls adjacent to cavitary lung lesions and similar fainter staining for IgG and IgA (DeHoratius et al. 1972) but complement studies have been positive only in the alveolar walls of patients with idiopathic pulmonary fibrosis (Turner-Warwick 1966, 1974; Turner-Warwick et al. 1971).

Vascular disease is found post-mortem in the lungs of rheumatoid patients (Gardner 1972) and the changes described in both pulmonary and bronchial arterioles include muscularization, medial hypertrophy, fibrosis and ablation (Cruickshank 1959; Heath et al. 1968). Pulmonary fibrosis also was present. Of the two autopsy studies on rheumatoid patients succumbing to pulmonary hypertension in the absence of fibrosis only Kay and Banik (1974) could find evidence of any arteritis and that was confined to the muscular pulmonary arteries. The patient described by Gardner et al. (1957) had Raynaud's phenomenon too and, at post-mortem, severe intimal fibrosis of both digital and pulmonary arteries.

Fibrosing alveolitis

The occurrence together of rheumatoid disease and fibrosing alveolitis is probably a disease association (Scadding 1969). The association is made more significant by the description of autoantibodies such as rheumatoid and antinuclear factors in cryptogenic fibrosing alveolitis (Tomasi et al. 1962; Nagaya et al. 1966; Turner-Warwick 1967). Familial clustering of rheumatoid arthritis and fibrosing alveolitis has been reported (Hilton & Pitkeathly 1974).

Whether fibrosing alveolitis occurs in rheumatoid subjects or alone it appears to have the same clinical and histological features. Though the presentation may precede the appearance of the arthritis (Thadani 1973) it is not uncommon for what would be dyspnoea on effort to be masked by the relative immobility of the arthritic patient. The high incidence of clubbing reported by Walker and Wright (1968) has not been seen by us. The youngest reported case is probably the girl of 9 years mentioned by Martel et al. (1968). The prognosis varies from a few months to many years (Ellman & Ball 1948; Patterson et al. 1965). Cor pulmonale may develop (Price & Skelton 1956; Patterson et al. 1965) but infections, even with opportunistic oranisms (Anderson et al. 1975), are probably the greatest contributor to the morbidity and mortality toll.

Conventional respiratory function tests have been used in attempts to show a correlation with alveolar wall thickness (Salorinne et al. 1975), seropositivity (Davidson et al. 1974; Whorwell et al. 1975; Schernthaner et al. 1976), and smoking habits (Frank et al. 1973; Davidson et al. 1974; Whorewell et al. 1975). Spirometry and volumetric tests are not very helpful and generally show no correlation with symptoms or chest radiographic appearances (Laitinen et al. 1975). Impaired diffusion was a common finding and may be out of proportion to the reduction in vital capacity. Haemoglobin correction of the observed diffusing capacity may not be necessary. Salorinne (1976) provides an excellent review of these aspects. Hypoxaemia at rest and/or unsaturation on excercise are more sensitive indicators of impaired pulmonary function (Frank et al. 1973), especially if plotted against oxygen comsumption (Crystal et al. 1976).

More recently attention has been focused on airway obstruction. Mild interstitial fibrosis of peribronchiolar areas can cause obstruction in progressive systemic sclerosis and the same process probably occurs in rheumatoid disease (Collins et al. 1976). Rheumatoid patients who are smokers have lower maximal mid-expiratory flow rates than either non-smoking rheumatoids or smokers with degenerative joint disease (Collins et al. 1976). A possible additional factor in causing lung damage is the presence of reduced concentrations of α_1 antitrypsin as associated with heterozygotes for the Z allele (Cox & Huber 1976). MZ and SZ (and possibly MS also) (Collins et al. 1976) are more commonly found in adult rheumatoid patients than in controls. These studies raise the possiblity that heterozygotes, especially for the Z allele, may have as greatly an increased predisposition to rheumatoid arthritis as to chronic obstructive pulmonary disease.

The diagnosis of fibrosing alveolitis is usually made clinically and may be supported by radiographs, respiratory function tests or lung biopsy. Radiologically the fibrosis is usually basal and even when generalized is usually denser in the lower zones. Predominantly upper lobe fibrosis has not been described in rheumatoid disease, though it has been reported in association with ankylosing spondylitis (Davies 1972). We have seen two rheumatoid patients with predominance in the upper zones and one other in whom there were upper lobe changes only.

Case 9. This man developed serpositive, nodular rheumatoid arthritis in 1962 when aged 40 years. Though a moderate smoker he had no respiratory symptoms when admitted in 1974 for control of continuing active joint disease. In addition there was no history of tuberculosis or any industrial exposure. Physical examination confirmed only the nodules and the arthritis and a few left upper zone crackles. A chest radiograph showed extensive left apical fibrosis. His Mantoux test was negative. An earlier chest radiograph in 1970 was unequivocally normal.

The certain exclusion of tuberculosis is difficult here. Unlike the case reported by Aronoff et al. (1955), where upper lobe fibrosis was accompanied by a strongly positive Mantoux test, extensive investigations in our patient have failed to reveal tuberculosis or other disorder. His HLA tissue type is 2, 9, 7, 14. We suggest that his case is the first reported association of sole upper lobe fibrosis and rheumatoid disease. It is of interest that Davies et al. (1975) have described five patients with upper lobe fibrosis of massive proportions with no disease association whatsoever.

Lung biopsy studies have confirmed that there are no differences between the histology of rheumatoid and idiopathic fibrosing alveolitis. Interstitial pneumonia has been used to describe some of the inflammatory changes seen (Cruickshank 1959) and Liebow (1975) makes a plea for the recognition and classification of interstitial pneumonia into five types on morphological grounds. Though desquamative (cellular) and mural (fibrotic) changes mark the ends of the spectrum many histological types are usually present in any one specimen (Cruickshank 1959; Scadding 1969; Crystal et al. 1976). Of potential help in both assessing and following the extent of pulmonary inflammation are the techniques of gallium-67 citrate scanning and bronchopulmonary lavage analysis which have been used in the management of patients with idiopathic pulmonary fibrosis (Crystal et al. 1976; Davis et al. 1976; Reynolds et al. 1977).

Shrinking lung

A gradual reduction in lung volume with a progressive rise of the diaphragms ('shrinking lung') occurs in systemic lupus erythematosus (Hoffbrand & Beck 1965). The next patient appears to exhibit this progression, but in the presence of unequivocal rheumatoid arthritis.

Case 10. A storeman born in 1910 developed classical seropositive, erosive, nodular rheumatoid arthritis in 1956. In 1969 gradual onset of dyspnoea was noted and it has been progressive since. No cardiac cause was found. Despite persistently active joint disease, the main problem is his disabling dyspnoea which is not associated with cough or phlegm. Respiratory function tests show a vital capacity of about half the predicted value and serial chest radiographs over the last 5 years show a progressive diminution in the size of the lung fields. His antinuclear factor, previously negative, is now positive but LE cells have never been found, serum complement levels are normal and he has no clinical stigmata of systemic lupus erythematosus.

Caplan's syndrome

As originally described, the syndrome encompasses rheumatoid arthritis, radiological evidence of pneumoconiosis after exposure to coal dust and multiple, often large, pulmonary nodules on the chest radiograph (Caplan 1953) and the syndrome has been expanded to include other dusts (see Scadding 1969). A high proportion of coal miners with pneumoconioses have a positive rheumatoid factor test (Soutar et al. 1974). Rheumatoid factor has been found in the lung nodules of some patients with pneumoconiosis (Wagner & McCormick 1967).

Amyloid

Amyloidosis of the lung in rheumatoid arthritis is possibly not as rare as the scarcity of reports might suggest (Tribe 1966). Most post-mortem studies on rheumatoid patients concentrate on other visceral involvement. Romicka and Maldyk (1975) identified amyloid in the arterioles of bronchial mucosa and lung parenchyma in three of 16 children dying from juvenile rheumatoid arthritis. The anatomical site of pulmonary amyloid deposition is not so clearly stated in the patients mentioned by Liebow and Carrington (1966), Wiman and Hofer (1974) or Williams (1974) but Tribe (1966) reported that amyloid deposition was most marked in the subpleural perialveolar tissue. No relationship of pulmonary amyloid to clinical findings, therapy, radiographic appearances or pulmonary function tests has been documented.

Drug effects

Diffuse pulmonary changes in rheumatoid patients may be caused by drugs. Winterbauer et al. (1976) report two patients with biopsy-proven reversible interstitial pneumonitis attributed to gold therapy. One of these patients had a seronegative polyarthritis and after recovery from the pulmonary injury developed renewed respiratory symptoms when rechallenged. A similar case with rechallenge, but no biopsy, is described by Geddes and Brostoff (1976). Their patient had a strongly positive lymphocyte transformation test to gold, unlike the cases of Winterbauer et al. (1976).

An almost identical reversible clinical picture of dyspnoea and dry cough with radiological diffuse alveolitis has been reported as a complication of D-penicillamine treatment (Eastmond 1976). In the patient described by Gibson et al. (1976) there was, in addition, an irreversible focal proliferative and crescentic glomerulonephritis, though the lung lesion disappeared after ventilatory assistance and therapy with azothioprine and corticosteroids. Immunofluorescent studies on the renal biopsy did not demonstrate any IgG or complement deposition. A possible mechanism for this presumed drug induced autoimmune phenomenon has been discussed by Maini and Roffe (1977).

COMBINED PLEURAL AND PULMONARY LESIONS

Combinations of lesions occur frequently in rheumatoid lung disease and nodules, especially, may coexist with pleurisy, pleural effusion or pulmonary fibrosis (Martel et al. 1968; Walker & Wright 1968). Cases from our own experience are outlined in Table I.

These cases exhibit early pleural changes followed later by fibrosing alveolitis. This progression is apparent in the reports of Horler and Thompson (1959), Frank et al. (1973), Steinberg (1975) and Yarborough et al. (1975).

THERAPY

Though it may be the treatment most often required, appropriate chemotherapy for infections is beyond the scope of this article. Attention is drawn to the need for more aggressive action in some pleural disorders where repeated aspiration or conservative therapy fails. Permanent empyema drainage has been advocated by Yarborough et al.

Table I. Mixed pleural and pulmonary involvement in rheumatoid disease

Case	*History*
Case 8, M, 52	1970: Acute pulmonary vasculitis at onset of rheumatoid arthritis (see text). Pleural shadow on radiograph 1972: Pulmonary nodules 1973: Pulmonary fibrosis 1975: Bronchopleural fistula
Case 11, M, 47	1969: Pleurisy 1971: Onset of rheumatoid arthritis 1974: Pulmonary fibrosis
Case 12, M, 52	1969: Onset of rheumatoid arthritis 1971: Pleural rub and pleural shadow on radiograph 1973: Onset of dyspnoea 1975: Progressive pulmonary fibrosis
Case 13, F, 32	1955: Onset of rheumatoid arthritis 1970: Pleural rub 1973: Pneumothorax. Pleural fibrosis found at decortication operation 1975: Pulmonary fibrosis

(1975), and recurrent pleural effusions and recalcitrant pneumothorax have been helped by decortication (Brunk et al. 1966; Walker & Wright 1967; Yarborough et al. 1975; Case 13).

Corticosteroids have a role in the management of acute pulmonary infiltrates as discussed earlier. Chronic pulmonary changes are more difficult to handle. Isolated reports of spontaneous improvement in chronic basal fibrosis (Martel et al. 1968) could jeopardize the assessment of drug therapy. Corticosteroids have no beneficial effect on the radiographic appearance or pulmonary function in rheumatoid patients with chronic diffuse infiltration (Thompson & Leathart 1965). D-Penicillamine has been useful in three patients (Lorber 1966) but there are no subsequent reports on this approach.

An examination of the therapies advocated for idiopathic fibrosing alveolitis proves interesting. Corticosteroids were considered unhelpful by Herbert et al. (1962) and Celga (1977), but beneficial by Malmberg et al. (1965) in those cases without radiological honeycombing. Combination therapy of prednisone with either azothioprine or D-penicillamine is beneficial in approximately two-thirds of patients but full details of the improvements were not published (Celga 1977). Cyclophosphamide and chlorambucil have been used in individual cases (Brown & Turner-Warwick 1971; Weese et al. 1975). A double-blind trial of prednisone plus/minus azothioprine in idiopathic fibrosing alveolitis is under way (Crystal et al. 1976). The relevance of any of these therapies to the control of diffuse alveolitis in rheumatoid disease has yet to be determined, despite the strong clinical similarities. Published reports on more heroic measures such as thoracic duct drainage have not documented any respiratory problems (Dumont et al. 1964; Wegelius et al. 1970; Paulus et al. 1973).

COMMENT

In the studies of Walker (1967) and Walker and Wright (1968) on 516 patients, pulmonary infections were twice as common in men as in women and pleural effusions 2.4 times as common. From 17 other published reviews of lung problems in rheumatoid disease, where the number and sex of patients is identified, the proportion of males to females is 105:43. Of the last 100 consecutive cases of lung involvement in the presence of rheumatoid arthritis referred to the Brompton Hospital 56 were male. Taking even this figure and a conservative estimate for the male/female ratio of rheumatoid arthritis in white European and North American populations of 3:4, then about twice as many rheumatoid men as women have pleural or pulmonary features. This is in accord with our own experience.

Other connective tissue diseases may have associated lung disorders, for example effusion, atelectasis and shrinking lung in lupus erythematosus, fibrosis in scleroderma, upper lobe fibrosis and cavitation in ankylosing spondylitis and nodules in Wegener's granulomatosis and polyarteritis nodosa. The diagnosis remains largely a clinical matter and depends on an awareness of the types of lung lesions that can be found.

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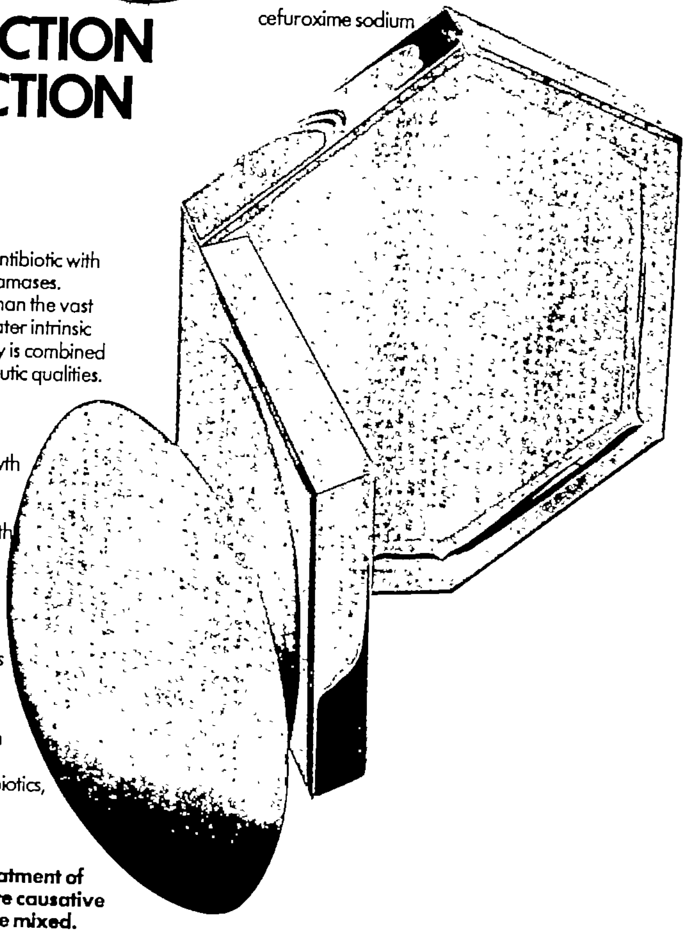

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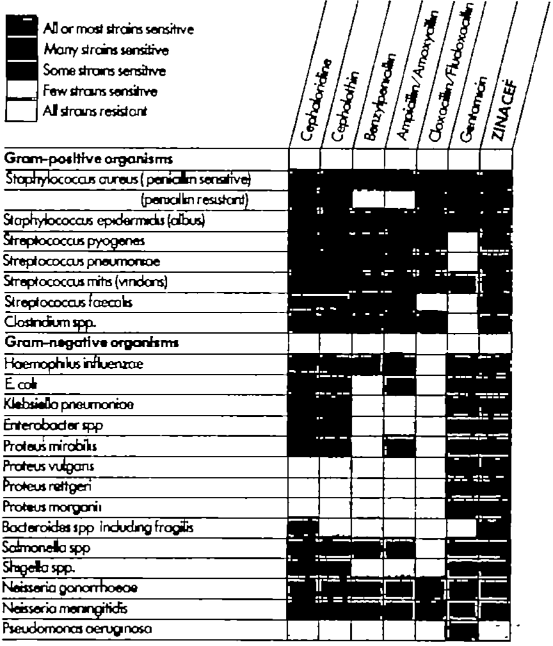

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■ Many strains sensitive
■ Some strains sensitive
□ Few strains sensitive
□ All strains resistant

	Cephaloridine	Cephalothin	Benzylpenicillin	Ampicillin/Amoxycillin	Cloxacillin/Flucloxacillin	Gentamicin	ZINACEF
Gram-positive organisms							
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(penicillin resistant)	■	■	□	□	■	■	■
Staphylococcus epidermidis (albus)	■	■	■	■	■	■	■
Streptococcus pyogenes	■	■	■	■	■	□	■
Streptococcus pneumoniae	■	■	■	■	■	□	■
Streptococcus mitis (viridans)	■	■	■	■	■	■	■
Streptococcus faecalis	■	■	■	■	□	□	■
Clostridium spp.	■	■	■	■	■	□	■
Gram-negative organisms							
Haemophilus influenzae	■	■	■	■	□	■	■
E. coli	■	■	□	■	□	■	■
Klebsiella pneumoniae	■	■	□	□	□	■	■
Enterobacter spp	■	■	□	□	□	■	■
Proteus mirabilis	■	■	□	■	□	■	■
Proteus vulgaris	□	□	□	□	□	■	■
Proteus rettgeri	□	□	□	□	□	■	■
Proteus morganii	□	□	□	□	□	■	■
Bacteroides spp including fragilis	■	□	□	□	□	□	■
Salmonella spp	■	■	■	■	□	■	■
Shigella spp.	■	■	□	□	□	■	■
Neisseria gonorrhoeae	■	■	■	■	■	■	■
Neisseria meningitidis	■	■	■	■	■	■	■
Pseudomonas aeruginosa	□	□	□	□	□	■	□

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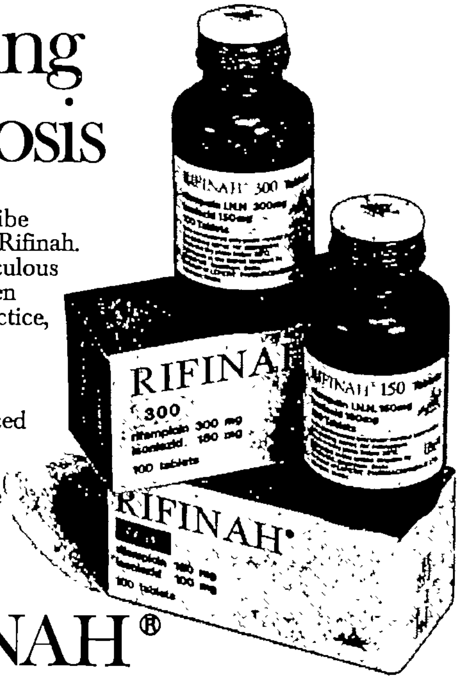

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Br. J. Dis. Chest (1978) *72*, 301

PULMONARY NECROBIOTIC NODULES WITHOUT RHEUMATOID ARTHRITIS

DENNIS ERAUT*, JOHN EVANS† AND MAXWELL CAPLIN

The London Chest Hospital

Summary

Pulmonary necrobiotic nodules are the least common of the pulmonary lesions associated with rheumatoid arthritis. Histologically they are identical to subcutaneous rheumatoid nodules. Systemic rheumatoid arthritis usually precedes the development of pulmonary nodules.

Seven cases where the pulmonary nodule appeared before or without the development of systemic rheumatoid arthritis are described. The typical histological and radiological features of necrobiotic nodules were found in each. In five of the seven the nodules were in more than one site and in five there were cavitating nodules. Spontaneous improvement occurred in one case. Pulmonary nodules preceded systemic rheumatoid arthritis in three cases and in the remaining four cases systemic rheumatoid arthritis has not yet appeared despite prolonged follow-up. In all patients, tests for rheumatoid factor have remained negative. The absence of circulating rheumatoid factor and systemic rheumatoid arthritis cannot exclude the diagnosis in these cases if the histological diagnosis is accepted as conclusive.

INTRODUCTION

Pulmonary necrobiotic rheumatoid nodules are rare manifestations of rheumatoid arthritis. About 50 cases have been reported in the literature (Panettiere et al. 1968; Thadani 1973). With two exceptions, long-standing systemic rheumatoid arthritis preceded the development of pulmonary necrobiotic nodules (Scadding 1969; Turner-Warwick 1969).

This paper presents the cases of seven patients in whom the typical histological and radiological features of necrobiotic nodules were found. In three, pulmonary nodules preceded the appearance of systemic rheumatoid arthritis by 11 years, 6 months and 3 months respectively. In four further cases, which have been followed for 3 to 26 years, titres of circulating rheumatoid factor have always been normal and systematic rheumatoid arthritis has not yet appeared.

Pulmonary necrobiotic rheumatoid nodules are defined as round pulmonary lesions histologically identical to subcutaneous rheumatoid nodules: they have an area of central collagen necrosis surrounded by a pallisade of histiocytes which is surrounded by granulation tissue consisting of plasma cells, lymphocytes and fibroblasts. Obliterative vas-

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culitis with endothelial proliferation is often seen, but fibrinoid necrosis is uncommon (Turner-Warwick 1969).

Case Report

The case of one patient (Case 1) is of special interest. The important details of other cases are shown on Table I.

A girl aged 19 presented in 1951 to the Metropolitan Chest Clinic with repeated small haemoptyses. Her chest radiograph was said to be normal. The following year she had further recurrent haemoptyses and tomograms revealed cavitation in the right lower lobe. Repeated examination of sputa and three bronchoscopies failed to reveal any tuberculosis.

In August 1953 administration of streptomycin and PAS was started. In September a right lower lobectomy and subsegmental resection of the anterior segment of the right upper lobe was carried out at the Brompton Hospital. Postoperatively a pneumoperitoneum was induced and was maintained for one year. She continued treatment with PAS and isoniazid for four years.

She moved to another area and attended the London Chest Hospital in 1957 because of repeated haemoptyses. Her chest radiograph now showed left upper lobe cavitation, which increased in size.

In February 1958 a left anterior segmental resection and lingulectomy was carried out. Histological examination showed caseation but no acid-fast bacilli. She continued taking PAS and isoniazid until 1960. After recovery she was very well and working full time.

In March 1963, still symptomless, her chest radiograph showed a fresh round nodule in the right mid-zone. Sputum was again negative for acid-fast bacilli. She was again given streptomycin, PAS and isoniazid. Some radiological improvement occurred. Two months later, in May 1963, she developed stiffness of the hands, elbows, knees and back, which was worse first thing in the morning, and mild swelling of the proximal interphalangeal joints. Investigations revealed an ESR of 16 mm/hour which increased to 43 mm hour by June. The latex fixation test was positive. LE cells were not present. Radiographs of the hands showed some tissue swelling, but no erosions. Rheumatoid arthritis was diagnosed and the histological findings of September 1953 and February 1958 were reviewed and found to be compatible with necrobiotic cavitating pulmonary rheumatoid nodules.

Five years later the chest radiograph still showed a small cavitating nodule in the right mid-zone, with no fresh nodules. A recent radiograph shows that the cavitated nodule has enlarged and there are now several other nodules. Her latex titre is positive at 1 in 80. The rheumatoid arthritis has given little trouble over the last ten years.

In summary, this is the case of a woman with multiple necrobiotic cavitating pulmonary rheumatoid nodules associated with systemic rheumatoid arthritis. The first cavitating nodule preceded the development of systemic rheumatoid arthritis by 11 years.

DISCUSSION

A review of the records of The London Chest and Brompton Hospitals has revealed 26 cases of pulmonary nodules associated with long-standing rheumatoid arthritis. In seven of these the rheumatoid nodules appeared in the lungs before any evidence of systemic rheumatoid arthritis . In one patient (Case 1) there was a gap of 11 years before any other rheumatoid disease, and in another (Case 4) 26 years have passed and there is still no evidence of any systemic rheumatoid arthritis.

Several different thoracic manifestations of rheumatoid arthritis have been described. The most common are pleurisy, pleural nodules, pleural effusions and fibrosing alveolitis (Walker & Wright 1968; Scadding 1969; Turner-Warwick 1969). Less common are intrapulmonary necrobiotic rheumatoid nodules and rheumatoid pneumoconiosis or Caplan's syndrome. (Caplan 1953; Caplan et al. 1962; Walker & Wright 1968; Panettiere et al. 1968; Scadding 1969; Turner-Warwick 1969). Occasionally there may be more

Table I. Summary of the patients

No.	*Sex*	*Age*	*Presentation*	*Chest radiograph*	*Initial diagnosis*	*Operation or treatment*	*Histology*	*Rheumatoid factor*	*Appearance of rheumatoid arthritis*
1	F	20	See text						
2	M	57	*1969*: symptom-free. Mass radiography referral	Round shadow apicoposterior segment left upper lobe	Bronchial carcinoma	Wedge resection	Necrobiotic rheumatoid nodule	Weakly positive	Six months later
3	M	62	*1977*: cough and haemoptysis	Two small nodules left lower lobe	Bronchial carcinoma	Left lower lobectomy	Rheumatoid nodule	Strongly positive	Three months later
4	M	42	*1949*: haemoptysis	Round shadow left lower lobe	? Pulmonary tuberculosis				
			1951	Second shadow right lower lobe	Pulmonary tuberculosis				
			1959: haemoptysis	Left lower lobe shadow increased	Pulmonary tuberculosis, sputum-negative	Wedge resection, antituberculous drugs 18 months	Presumed tuberculous		
			1975: haemoptysis	Left lower lobe shadow reappeared	?		Histology reviewed, necrobiotic rheumatoid nodule	Negative	No
5	M	67	*1973*: left chest pain	3 cm cavity with fluid level in posterior segment right upper	?	Wedge resection	Cavitating necrobiotic rheumatoid nodule	Negative	No
6	F	43	*1964*: general malaise	Cavity right upper lobe	Pulmonary tuberculosis, sputum-negative	Antituberculous drugs			
			1967	Shadow right upper lobe	?	Right upper lobectomy	Necrobiotic rheumatoid nodule	Negative	No
7	M	39	*1968*: cough	Cavitating lesion left lower lobe	Bronchial carcinoma	Left lower lobectomy	Necrobiotic rheumatoid nodule	Negative	No
			1970	Small round nodule right lower lobe					

than one pulmonary manifestation in the same patient; for example intrapulmonary nodules and a pleural effusion (Portner & Gracie 1966; Stengel et al. 1966; Scadding 1969). Three cases have been described with the combination of necrobiotic nodules, pulmonary fibrosis and pleural effusions (Flatley 1959; Cudkowicz et al. 1961; Thadani 1973).

In patients with known rheumatoid arthritis intrapulmonary nodules are rare. Aronoff et al. (1955) surveyed 253 patients, and Patterson et al. (1965) 702 patients but found no intrapulmonary nodules. Hooler and Thompson (1959) found one patient out of 182 studied, and Walker and Wright (1968) found only two in a survey of 516 patients. Caplan (1953) first described multiple, round, well defined opacities in a very small group of miners who claimed pneumoconiosis disability benefit. The condition was found in coal-miners who had clinical evidence of rheumatoid arthritis. The nodules were multiple, usually bilateral and 0.5–5 cm in size. Later similar nodules were described in rheumatoid patients exposed to other dusts including asbestos and silica (Tellesson 1961). Caplan (1962) later described a type of coarse generalized nodular pattern with irregular opacities. In these groups a high proportion had definite rheumatoid arthritis and nearly half of those without arthritis had circulating rheumatoid factor.

Maher (1954) and Christie (1954) were the first to observe intrapulmonary nodules in patients with no pneumoconiosis. Intrapulmonary nodules vary in size between 0.5 and 7 cm. They found most frequently in the upper and middle zones. Panettiere et al. (1968) and Walker and Wright (1968) reviewed the published cases and showed that about half had cavitated. A single nodule may look like a carcinoma or a tuberculous lesion. Often a number of nodules are found. They may resolve spontaneously and may recur, or they may appear first in one lung and then in the other. A single nodule may slowly enlarge and then others with or without cavities may appear around it. There are reports of rupture to cause a pneumothorax (Basten et al. 1966) and pyopneumothorax (Hindle & Yates 1965; Davies 1966).

Rheumatoid arthritis is more common in women, but pulmonary nodules have been reported more frequently in men. Small lesions give rise to no symptoms and even large lesions may not cause symptoms. Patients may, however, present with cough or haemoptysis and if there is pleural involvement there may be pain or breathlessness with an effusion (Panettiere et al. 1968; Walker and Wright 1968; Scadding 1969; Turner-Warwick 1969).

A high proportion of patients with intrapulmonary nodules also have subcutaneous nodules, the histology in the two being identical (Walker & Wright 1968). Nodules have been found especially in the heart. Titres of rheumatoid factor are usually high but, especially in the early stages, rheumatoid factor may be absent or present only in low titre (Panettiere et al. 1968; Turner-Warwick 1969). Where rheumatoid factor is initially negative it may later become positive.

The appearance of nodules on a chest radiograph, particularly in the absence of a history of rheumatoid arthritis, may give rise to diagnostic difficulties. The original diagnosis is often thought to be either carcinoma or tuberculosis. Hart (1966) reported one nodule eroding adjacent ribs where radiographs strongly suggested an invasive carcinoma. Other conditions which may give rise to solitary or multiple nodules which may cavitate are pneumoconiosis, systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, sarcoid, gumma, fungal infections such as histoplasmosis, and aerobic or anaerobic necrotizing pneumonias. Rarely histological examination will reveal primary pulmonary amyloid, a plama-cell granuloma or pulmonary hyalinizing granuloma (Engleman et al. 1977).

The absence of circulating rheumatoid factor does not exclude the diagnosis of a pulmonary necrobiotic rheumatoid nodule. Titres of circulating rheumatoid factor in all the cases described here, and in the one reported by Scadding (1969), have remained negative until systemic rheumatoid arthritis developed. Problems may arise as these nodules may disappear and reappear in different sites, with no relation to the course of systemic rheumatoid arthritis. In the absence of systematic rheumatoid arthritis and a positive titre of circulating rheumatoid factor histological examination is required for the diagnosis.

No therapy influences rheumatoid pulmonary nodules.

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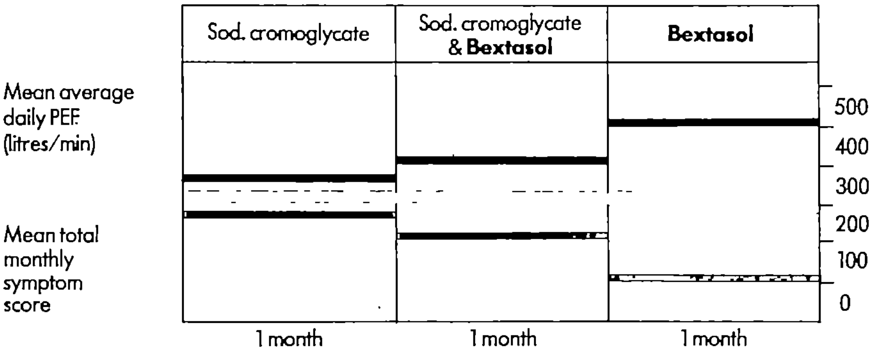

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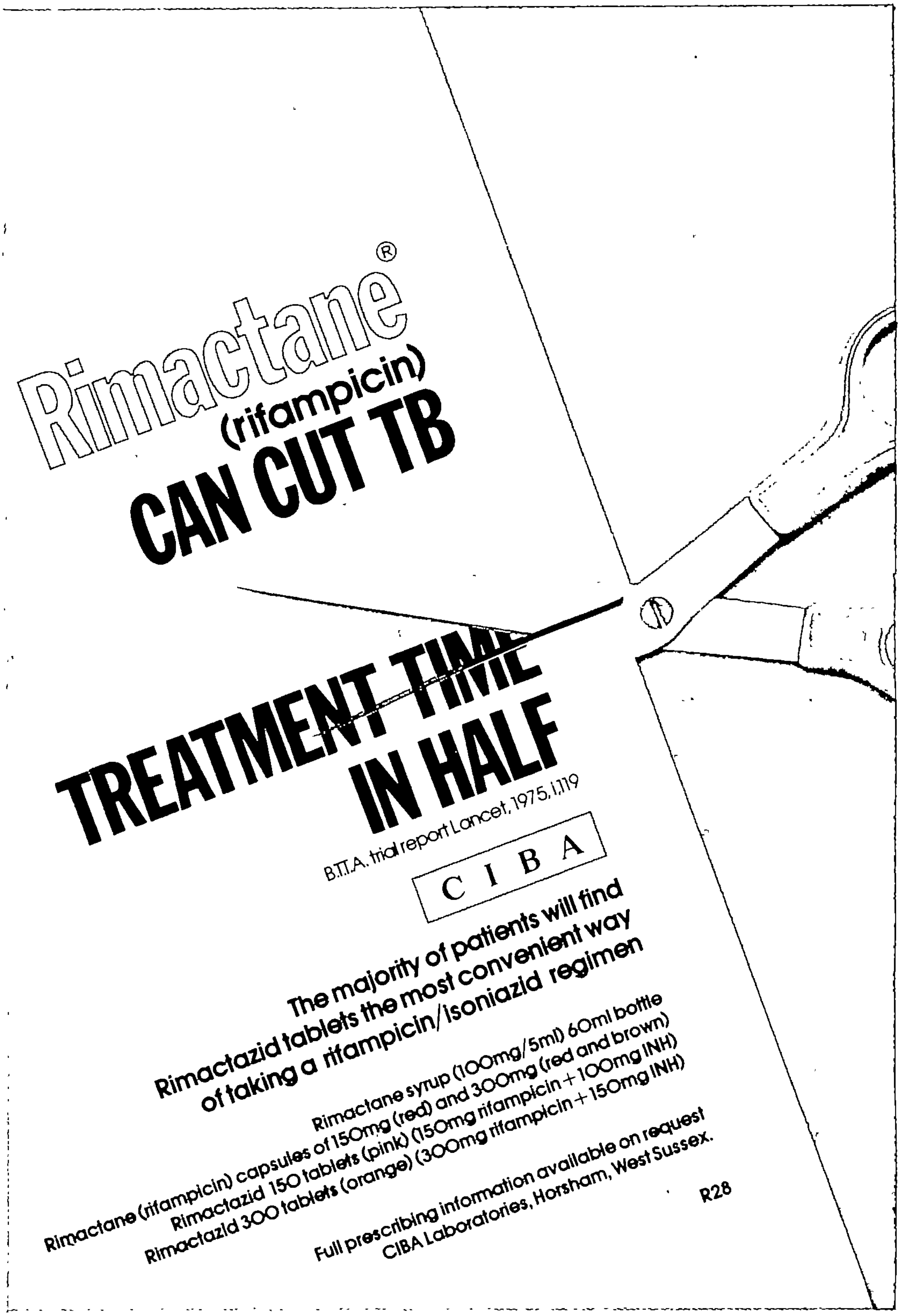

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BROMHEXINE IN SEVERE ASTHMA

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and K. B. Saunders

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Summary

Fourteen patients with acute severe asthma necessitating hospital admission were all treated with a standard therapeutic regimen, and in addition received either bromhexine or placebo (initially intravenously and subsequently orally) double-blind. We were unable to show any significant improvement in the rate of recovery of the bromhexine-treated group, in terms of either arterial blood gases or change in peak expiratory flow rates.

INTRODUCTION

Severe acute asthma (status asthmaticus) is a medical emergency and an indication for immediate admission to hospital (Leading Article, *British Medical Journal* 1975). Treatment consists of providing adequate oxygenation, effective bronchodilator therapy, corticosteroids and fluid replacement.

Autopsy examination of lungs taken from patients who have died in an attack of severe asthma shows the presence of widespread plugging of small airways with inspissated mucus (Dunnill 1971) and indeed these mucus casts are also found in the lungs of patients with quiescent asthma who have died of other unrelated causes (Dunnill 1965). Whether or not this mucus plugging can be relieved by physiotherapy is not known but vigorous encouragement to cough has been recommended in a recent review of the treatment of status asthmaticus (Stark 1972).

Bromhexine is a mucolytic agent that has been shown to decrease sputum viscosity (Palmer et al. 1970; Bürgi & Makin 1971) and is claimed to produce some benefit in patients with chronic bronchitis (Gent et al. 1969). It would seem reasonable to suppose that this drug might have a mucolytic effect on the inspissated mucus plugs present in severe asthma, and thus produce a more rapid recovery from the acute attack. We have therefore carried out a double-blind controlled trial to assess the effect of bromhexine in the treatment of acute severe asthma.

Patients and Methods

Fourteen consecutive patients admitted to the Middlesex Hospital with acute severe asthma all received a standard therapeutic regimen. The clinical details of these patients are given in Table I.

The treatment regimen used has already been described in detail elsewhere (Saunders 1974), and consists of the following:

1. Intravenous aminophylline 7 mg/kg on admission and repeated at 4 hours.

---

*Present address: Hammersmith Hospital, Du Cane Road, London W12 0HS

Table I. Details of patients on admission

Patient no.	*Sex*	*Age*	*Duration of asthma* (years)	*Length of present attack*	*Pretreatment PEFR*		*Pulse*	*Parodox*	Pao$_2$ (kPa)	Paco$_2$ (kPa)	pH
					(litres/min)	(% predicted)					
1	F	20	15	5 days	60	13	154	+	6.40	5.20	7.46
2	F	49	29	2 days	70	15	128	—	7.20	3.13	—
3	F	63	4	3 days	65	15	120	+	6.67	6.67	7.32
4	F	61	2	4 days	60	14	88	—	8 27	5.87	7.37
5	F	45	10	6 hours	20	4	126	—	8 67	6.20	7.28
6	M	30	6	5 hours	50	8	154	+	7 07	6.93	7.31
7	F	58	23	2 days	95	22	94	—	9.07	5.00	7.40
8	F	52	20	1 day	75	16	120	—	7.00	6.73	7.31
9	F	69	5	17 hours	65	16	124	—	5.73	6.20	7.40
10	F	58	30	11 hours	60	14	120	—	7.47	5.60	7.42
11	F	37	8	2 days	65	13	120	+	9.47	5.53	7.38
12	M	62	6	3 days	80	15	140	+	6.40	5.07	7.30
13	M	48	18	10 days	80	15	76	—	9.33	5.93	7.40
14	F	64	13	1 day	95	22	88	—	7.13	5.87	7.34

2. Intravenous hydrocortisone 4 mg/kg on admission and repeated at 4 and 8 hours; oral prednisone is started at 8 hours and continued at a dose of 60 mg/day thereafter.
3. Administration of a broad-spectrum antibiotic (cotrimoxazole 2 tablets twice daily, or ampicillin 500 mg four times daily in cases of sulphonamide sensitivity).
4. Rehydration with 2 litres of 5% dextrose over 24 hours.
5. Continuous oxygen delivered through an MC mask (or 28% Ventimask if arterial blood carbon dioxide tension, $P\text{aco}_2$, rises) for 24 hours or until arterial oxygen tension, $P\text{ao}_2$ (breathing room air), is greater than 8.6 kPa.
6. Oral salbutamol 4 mg three times daily.
7. Nebulized 0.5% salbutamol solution given by intermittent positive pressure ventilation (Bird ventilator) 12-hourly.

All patients were encouraged to cough up any sputum or secretions, but in order to achieve 'standard' physiotherapy, there was no tipping or percussion by the physiotherapist unless there was obvious collapse or consolidation and the patient was unable to expectorate unaided.

Bromhexine (or placebo) ampoules were added to the intravenous infusion so as to give a dose of 48 mg in the first 24 hours, and thereafter oral bromhexine (or placebo) was given in a dose of 24 mg three times daily for the remainder of the admission. Whether a patient had received active drug or placebo was not known until the code was broken on completion of the trial.

All patients had arterial blood gases measured on admission before the institution of any therapy, and further measurements were made routinely at 1, 8, 24 and 48 hours after admission, and again at the end of one week. Some of the patients had further blood gas analyses performed according to clinical indication. $P\text{ao}_2$, $P\text{aco}_2$ and pH were measured on standard Radiometer electrodes which were calibrated immediately before and after every sample.

Peak expiratory flow rates (PEFRs) were measured on admission, at 1 hour after institution of therapy, and at 4-hourly intervals for the first 24 hours. Thereafter PEFR was measured four times daily (before and after treatment with the Bird). If the PEFR was less than 200 litres/min on a standard Wright peak flow meter, a paediatric peak flow meter was used.

The weight of sputum expectorated daily was measured.

RESULTS

All results for the two groups (bromhexine-treated and placebo-treated) were assessed for statistical significance by Student's *t*-test for unpaired data. There was no significant difference between the two groups on admission in terms of blood gases or peak flows (expressed as actual PEFR, PEFR as a percentage of predicted normal or PEFR as a percentage of maximum attained throughout admission) (Table II).

The results of the mean blood gases for the two groups are shown in Table III. Although the placebo group have a higher mean $P\text{aco}_2$ at 1, 8, and 24 hours, this difference

Table II. Mean data on the two treatment groups on admission

	Bromhexine group	*Placebo group*
Age (years) (mean and range)	47.7 (20 – 62)	54.6 (37 – 69)
Sex distribution	5 F, 2 M	6 F, 1 M
$P\text{ao}_2$ (kPa) (Mean ± S.E.)	7.64 ± 0.41	7.51 ± 0.52
$P\text{aco}_2$ (kPa) (Mean ± S.E.)	5.69 ± 0.27	5.72 ± 0.45
PEFR (litres/min) (Mean ± S.E.)	60.7 ± 8.9	73.6 ± 4.2
PEFR as % of predicted normal (Mean ± S.E.)	12.9 ± 2.2	16.0 ± 1.1
PEFR as % of maximum attained (Mean ± S.E.)	23.0 ± 5.1	32.0 ± 2.8

There is no significant difference between the mean blood gases or peak flows of the two groups.

Table III. Arterial blood gases in the two treatment groups (mean ± S.E.)

	Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)	
	Bromhexine	*Placebo*	*Bromhexine*	*Placebo*
On admission	7.64±0.41	7.51±0.52	5.69±0.27	5.72±0.45
1 hour*	17.07±2.71	14.93±1.15	5.16±0.24	5.73±0.38
8 hours*	16.27±2.50	15.06±1.19	5.08±0.15	5.40±0.53
24 hours	7.73±0.48	8.21±0.76	4.87±0.28	5.05±0.52
48 hours	8.60±0.40	8.37±0.55	5.07±0.24	5.07±0.28
1 week	9.99±0.68	9.19±0.71	4.92±0.16	5.25±0.13

There was no significant difference between the two treatment groups at any time.
* Samples taken whilst patients were receiving oxygen. All other values taken whilst patients breathing room air.

is not statistically significant, nor is the higher mean Pa_{O_2} in the bromhexine group at the end of one week.

Fig. 1 shows the mean PEFRs (expressed as a percentage of predicted normal) for the two groups, and although the bromhexine group start with the lower mean PEFR and end with the higher, at no time do the difference between the two groups attain significance at the 5% level. Analysis of the data to show improvement in PEFR as percentage increase of initial value over the first 24 hours still fails to reveal any difference between the two groups.

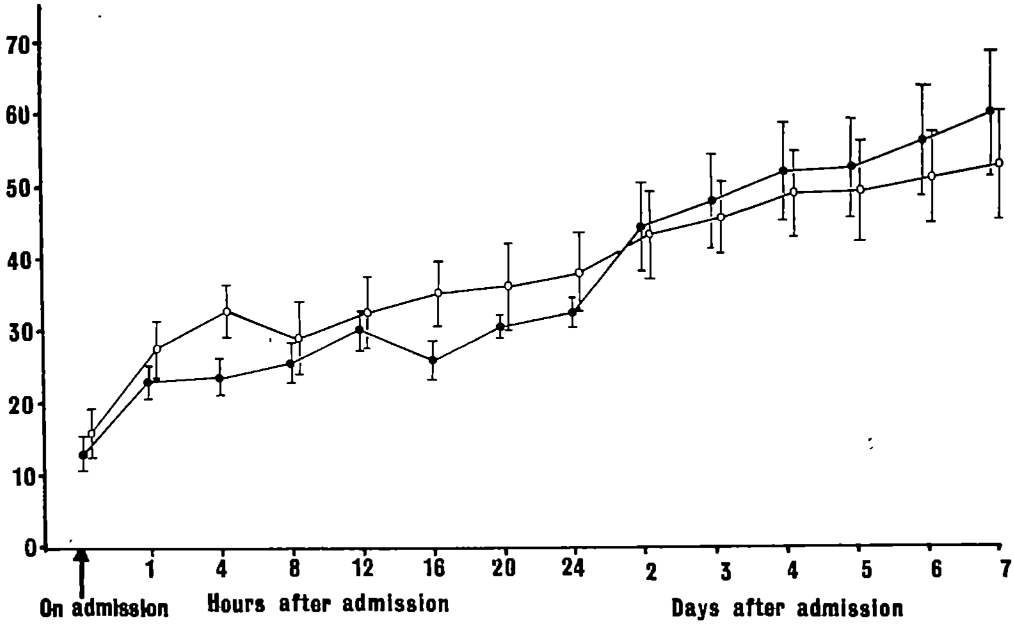

Fig. 1. Mean PEFRs as a percentage of predicted normal for the two treatment groups. Bars represent ± S.E. ● Bromhexine group. ○ Placebo group. There were no significant differences between the two groups

Apart from one patient in the bromhexine group who produced up to 80 g of sputum daily, there were no differences between the two groups in terms of sputum production, and indeed six of the patients failed to produce any sputum at all.

DISCUSSION

This double-blind controlled trial shows clearly that, in the dosage used, bromhexine produces no statistically significant improvement in the rate of recovery from severe asthma as assessed by arterial blood gases or changes in PEFR. Yet theoretically asthma, with its characteristically highly viscid bronchial secretions, ought to be one condition where effective mucolytic therapy might be expected to be beneficial. The high viscosity of the sputum of asthmatics is due to the presence of both deoxyribonucleic acid fibres and acid mucopolysaccharde fibres. Bromhexine produces rarefaction and fragmentation of the acid mucopolysaccharide fibres, but has no effect on the deoxyribonucleic acid fibres (Bürgi 1965). Deoxyribonucleic acid fibres (which are usually due to the presence of infection) are eliminated by antibiotics (Bürgi 1965; Bürgi & Makin 1971) and as all the patients in this study received broad-spectrum chemotherapy this cannot be the reason why bromhexine failed to produce an appreciable effect.

The results of previous studies of bromhexine in patients with chronic bronchitis have yielded conflicting results (Hamilton et al. 1970; Langlands 1970; Research Committee of the BTTA 1973; Gent et al. 1974), but it would appear that what objective evidence there is of improvement in airways obstruction by and large is found only in patients with mildly impaired ventilatory function, and that a chronic bronchitic with an FEV_1 of less than 1 litre is unlikely to be helped by bromhexine. All the patients in our study had severe airway obstruction (PEFR less than 100 litres/min), and it may be that mucolytic therapy in chest disease is likely to be beneficial only when airways resistance is not already grossly increased due to other mechanisms. In our patients it is possible that the effects of bronchospasm and mucosal oedema greatly exceeded those of inspissated mucus, and that even really effective mucolytic therapy is unlikely to be helpful at such an advanced stage of dysfunction. Nevertheless, although the only measurement we made of sputum was the amount expectorated each day (and many of the patients may well have swallowed their secretions), we were surprised that four of the bromhexine-treated patients failed to produce any sputum at all.

Another possible explanation for bromhexine being of no obvious benefit in this trial is that in status asthmaticus, by the time the patient reaches hospital the bronchi are already blocked with solid mucous plugs which, unlike thick viscous fluid, may well be totally unaffected by even the most potent mucolytic agents at present available.

Palmer (1973) has advocated the routine administration of bromhexine to all patients with severe asthma. As a result of our study we feel we are not able to support this recommendation.

ACKNOWLEDGEMENTS

We are indebted to Dr F. H. Scadding and Professor S. J. G. Semple for permission to study patients admitted under their care, and to Miss H. Hill for supervising physiotherapy and treatment with the Bird. We are grateful to Boehringer Ingelheim Ltd for supplies of bromhexine and for a generous grant towards equipment. During the period of this study M. R. was supported by a Sir Jules Thorn Research Fellowship.

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PULMONARY ALVEOLAR PROTEINOSIS: ANALYSIS OF PULMONARY WASHINGS

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Summary

Bronchopulmonary washings from a patient with pulmonary alveolar proteinosis who underwent therapeutic pulmonary lavage were examined. There were large amounts of protein and lipids of which main classes were phospholipid, cholesterol and free fatty acid. The major component of phospholipids recovered from the washings was lecithin rich in palmitic acid. We also found a high IgG level in the washings.

Both the findings of free cholesterol in high concentration in the washings and the electrophoretic pattern of protein in the washings suggested that the alveoli-filling material of our patient was not wholely derived from passive transudation of plasma constituents.

INTRODUCTION

Pulmonary alveolar proteinosis has been reported with increasing frequency since it was first described by Rosen et al. (1958). The cause of the disease remains unknown. The clinical course of the disease ranges from a spontaneous remission to a progressive form (Rosen et al. 1958; Levine 1962; Sanders et al. 1962; Larson & Gordinier 1965; Davidson & Macleod 1969). Until recently relatively little information was available on the biochemical composition of the accumulated intra-alveolar material.

The purpose of this study was to examine bronchopulmonary washings from a patient with pulmonary alveolar proteinosis who underwent therapeutic pulmonary lavage.

Case Report

A 27-year-old man was admitted to the Osaka University Hospital on 25 September 1974 with a 6-month history of non-productive cough and progressive dyspnoea on exertion. Exposure to occupational dusts or toxins was denied. He had smoked one pack of cigarettes daily for 5 years. The patient had normal temperature and blood pressure. The respiratory rate was 32/min, and pulse rate 88/min. No lymph nodes were palpable. Chest examination revealed a few basilar râles bilaterally. Cardiac examination was entirely unremarkable. No organs were enlarged, and peripheral oedema and clubbing were absent. Blood examination, erythrocyte sedimentation rate and urinalysis were normal. All biochemical investigations were negative except for a slight increase of serum lactic dehydrogenase activity. The purified protein derivative tuberculin skin test was positive. The chest radiograph showed diffuse, bilateral, finely granular infiltrates most prominent in the lower lung fields (Fig. 1). Microscopic examination and cultures of multiple sputum specimens demonstrated no acid-fast bacilli or other pathogens. The electrocardiogram was normal. Pulmonary function studies revealed a slight restrictive ventilatory impairment (VC 64% predicted, FEV_1 86% VC). Blood gas determinations made while the patient was breathing room air showed: arterial $P\text{O}_2$ 54 mmHg, arterial $P\text{CO}_2$ 32 mmHg and pH 7.43.

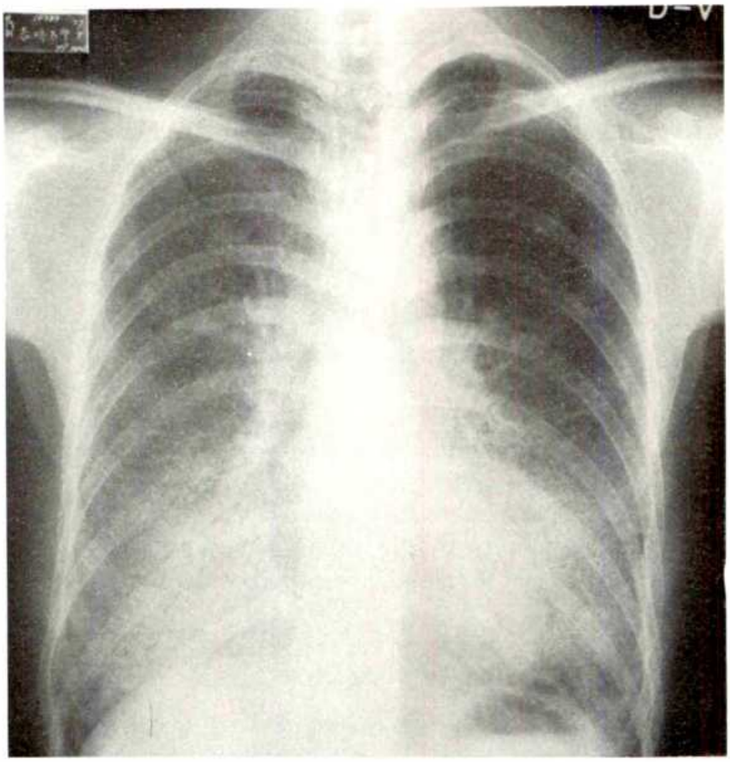

Fig. 1. Chest radiograph taken before pulmonary lavage, showing diffuse, bilateral, finely granular infiltration

An open-lung biopsy was performed on 14 October 1974 to establish the diagnosis. The biopsy specimen showed the alveoli to be filled with a granular, dense eosinophilic, proteinaceous material and normal alveolar septa, consistent with the diagnosis of pulmonary alveolar proteinosis. Three weeks later the patient was treated with therapeutic pulmonary lavage of the left lung. Four weeks after the pulmonary lavage the patient was discharged with improvement in symptoms, in hypoxaemia and in the chest radiograph findings. This remission lasts for 18 months after the pulmonary lavage (Fig. 2).

Materials and Methods

Pulmonary lavage

The left lung of the patient was lavaged with 2 litres of isotonic saline which contained 7.5 units of heparin per ml and 1% acetylcysteine, using the modified procedure of Ramirez-R et al. (1965).

Extraction and analysis of pulmonary washings

The first 800 ml of lavage fluid was obtained immediately after the lavage procedure and centrifuged at 800 *g* for 10 min to remove minor solid elements. The supernatant fluids were referred

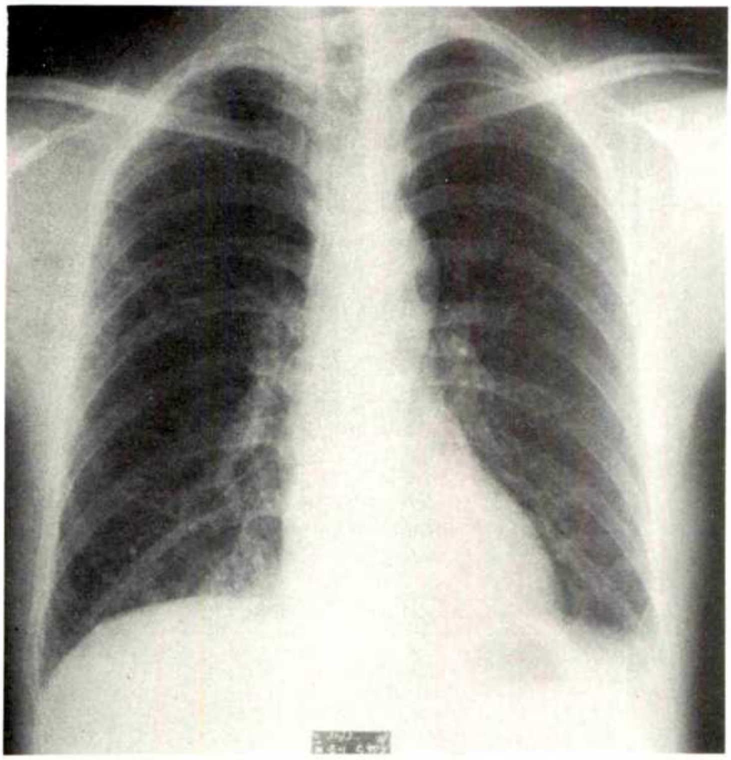

Fig. 2. Chest radiograph taken 18 months after pulmonary lavage of the left lung, showing clearing of left side with shadowing in the right lower zone

to as pulmonary washings and used for analysis of protein and lipids. Aliquots of the pulmonary washings were extracted for lipids by the method of Folch et al. (1957). Total lipid was determined gravimetrically, after evaporation of the solvents at 40°C under reduced pressure to constant weight. The lipid residue was dissolved in an appropriate volume of chloroform/methanol (2/1, v/v) and used for the determinations of total phospholipid phosphorus, free and total cholesterol, and triglyceride according to the methods of Bartlett (1959), Leffier and McDougald (1963) and Fletcher (1968) respectively. Free fatty acid was also determined by the procedure of Dole and Mernertz (1960). Phosphatide fractions of the pulmonary washings and serum from the patient were separated by thin-layer chromatography on silica gel G plates using the developing system of chloroform/methanol/water (65/25/4, $v/v/v$). For quantification of phosphatide fractions, the area of silica containing each fraction was marked by exposing the plates to iodine vapors and scraped into a test tube. The scraped fractions were analysed using the method of Bartlett (1959) to determine the phospholipid phosphorus. An aliquot of lecithin fraction of the washings obtained by thin-layer chromatography was transmethylated using diasomethane. Fatty acid methyl esters thus prepared were analysed by hydrogen flame gas–liquid chromatography with a glass column (0.4 × 150 cm) packed with 1% SE-30 silanized with chromosorb W. The peaks of fatty acids were identified by comparing their retention time with those of standard fatty acids.

Protein determinations

Quantitative determinations of total protein in the pulmonary washings from the patient were carried out by the method of Lowry et al. (1951) using bovine albumin as the standard. An aliquot of the pulmonary washings was concentrated approximately 200-fold by dialysis using polyethylene glycol (molecular weight 20 000). Albumin, alpha$_1$, alpha$_2$, beta, and total gamma globulins were determined by cellulose acetate electrophoresis of the concentrated washings and serum and read on a Jooko Densitron model PAN Densitometer. Estimations of immunoglobulins IgG, IgA, and IgM were made on the concentrated washings and serum by the standard technique (Mancini et al. 1965) of radial immunodiffusion using purchased Tripartigen plates. Quantitative IgE levels in the concentrated washings and serum were measured by the method of Johansson et al. (1968) using the Phadebas IgE test kit.

RESULTS

As shown in Table I, the pulmonary washings from the pulmonary alveolar proteinosis contained large amounts of protein and lipids. It seemed that the three main lipid classes were phospholipid, cholesterol and free fatty acid. The phospholipid content was 26% of the total recovered lipid. Free cholesterol was predominant and comprised about 80% of total cholesterol in the washings.

Table I. Composition of pulmonary washings

Constituent	*Amount* (mg/100 ml)
Total lipid	21.5
Total phospholipid	5.6
Total cholesterol	5.9
Free cholesterol	4.7
Free fatty acid	4.9
Triglyceride	1.8
Total protein	770.0

The per cent distribution of the several phospholipids in the washings and serum from the patient with pulmonary alveolar proteinosis is presented in Table II. Lecithin, which is the main phospholipid present in normal pulmonary surfactant, was the primary phospholipid (49%) in the washings, although it was in proportionally lower amount than that in serum.

Table II. Phospholipid analysis of pulmonary washings and serum (% of total phospholipid)

Phospholipid	*Pulmonary washings*	*Serum*
Lysolecithin	17.8	13.5
Sphingomyelin	24.9	17.2
Lecithin	48.8	62.9
Phosphatidylethanolamine	8.5	6.4

The fatty acid pattern of lecithin recovered from the pulmonary washings is shown in Table III. The major moiety of lecithin fatty acid was palmitic acid (55%).

Table III. Fatty acid esters of lecithin in pulmonary washings (% of lecthin fatty acids)

Ester	*Composition* (%)
Myristic acid (14:0)	3.3
Palmitic acid (16:0)	55.5
Palmitoleic acid (16:1)	2.1
Stearic acid (18:0)	18.1
Oleic acid (18:1)	18.9
Linoleic acid (18:2)	—
Arachidonic acid (20:4)	2.1

Cellulose acetate protein electrophoresis of the concentrated pulmonary washings and serum is demonstrated in Table IV. There was a relative increase in the gamma globulin concentration in the pulmonary wahings as compared to serum of the patient with pulmonary alveolar proteinosis.

Table IV. Protein electrophoresis of concentrated pulmonary washings and serum

Protein	*Patient's pulmonary washings*	*Patient's serum*	*Normal serum*[*]
Gamma globulin	27.0	12.2	13.1 ± 1.9
Beta globulin	8.0	5.4	7.9 ± 1.4
Alpha-2 globulin	8.9	8.0	7.9 ± 1.4
Alpha-1 globulin	4.2	1.0	2.7 ± 1.4
Albumin	51.9	73.4	67.5 ± 3.5

[*] Cellulose acetate electrophoresis. Values expressed as percentage of total protein. Normal values are Mean ± SD.

There was an approximately 9-fold increase in the percentage of total protein represented by IgG as compared to that represented by IgA (Table V). IgE was not detected in the concentrated pulmonary washings from the patient with pulmonary alveolar proteinosis.

Table V. Immunoglobulins in concentrated pulmonary washings

Immunoglobulin	*Amount* (%)
IgG	112.7
IgA	12.9
IgM	10.6
IgE	undetectable

Values expressed as percentage of total protein measured in the original pulmonary washings.

The levels of serum immunoglobulins of the patient with alveolar proteinosis were almost normal except for a slight decrease of IgA (Table VI).

Table VI. Immunoglobulin concentrations in the serum of the patient

Immunoglobulin	*Patient's serum*	*Normal serum*
IgG (mg/100 ml)	1380	1330 ± 150*
IgA (mg/100 ml)	129	300 ± 50*
IgM (mg/100 ml)	158	138 ± 50*
IgE (units/ml)	78	1000–500†

* Mean ± SD.
† Range in our laboratory.

DISCUSSION

Pulmonary alveolar proteinosis is an uncommon disease characterized by the accumulation of the lipid-rich proteinaceous material in the alveoli (Rosen et al. 1958; Ramirez-R & Harlan 1968). The source of this material has not been established, although there have been considerable speculations about this (Rosen et al. 1958; Larson et al. 1965; Stansifer & Bourgeois 1965; Hawkins et al. 1967; Ramirez-R & Harlan 1968; Rupp et al. 1973). McClenahan and Mussenden (1974) suggested that the intra-alveolar material in alveolar proteinosis represents an accumulation of modified normal surfactant and serum, rather than abnormal lipids or proteins or disproportionate quantities of normal lipids.

In the present study, the pulmonary washings from the patient with pulmonary alveolar proteinosis contained large amounts of protein and lipids. Compared with the patients with pulmonary alveolar proteinosis described by Ramirez-R and Harlan (1968), in our patient the total lipid content of the washings accorded with those from remission forms, but the total protein content of the washings was equivalent to those from relapse or progressive forms. So it seems difficult to asssess the severity or prognosis of this patient from these data.

Phospholipids, especially dipalmitoyl lecithin, are major components of the surface-active material (surfactant) that lines the alveolar membrane and serve to lower surface tension at the air–alveolar interface thereby preventing collapse of the alveoli of the lung (Clements 1970). In the patient in our study the presence of large amounts of lecithin rich in palmitic acid was demonstrated, which is in good agreement with the previous reports (Ramirez-R & Harlan 1968; Ramirez-R et al. 1971; McClenahan & Mussenden 1974; Sahu et al. 1976). In contrast to data described by Ramirez-R et al. (1971) and Sahu et al. (1976), lecithin in the washings from our patient did contain a small amount of arachidonic acid. It may be considered that the distribution of the minor moiety of lecithin fatty acids in the washings is variable from patient to patient with pulmonary alveolar proteinosis.

The content of total cholesterol in the washings from our patient with pulmonary alveolar proteinosis was similar to those reported previously (Ramirez-R & Harlan 1968; McClenahan & Mussenden 1974). Furthermore, free cholesterol was predominant and comprised about 80% of total cholesterol, which is nearly the same as the observation of Sahu et al. (1976).

In addition to the predominant presence of free cholesterol, the protein electrophoretic pattern of the washings from our patient suggested that the alveolar filling material was not the result of simple transudation of plasma constituents.

Rupp et al. (1973) have described a selective increase of IgG in the pulmonary washings from all their five patients with pulmonary alveolar proteinosis, and a lesser increase of IgA, suggesting either a local production or a mechanism for concentrating these immunoglobulins. We also found a high IgG level in the concentrated pulmonary washings, and the ratio of IgG to IgA in the washings was far greater than those in the concentrated bronchial fluid from normal non-smokers and smokers reported by Reynolds and Newball (1974). The significance of the elevated IgG level in the pulmonary washings from this patient remains unknown.

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BLEOMYCIN LUNG DAMAGE: THE PATHOLOGY AND NATURE OF THE LESION

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Summary

The pathology of two cases of pulmonary damage due to bleomycin is described. The drug damages the alveolar walls. A sequence of pathological changes could be traced commencing with oedema, intra-alveolar fibrin and haemorrhage, followed by type II pneumocyte hyperplasia associated with bronchial epithelial squamous metaplasia. This led to intra-alveolar and alveolar wall collagen formation producing diffuse interstitial fibrosis with microcyst formation associated with cuboidalization of the epithelium.

These changes are similar to those seen in experimental bleomycin damage in mice, where it has been shown that the changes are the result of vascular damage and type I pneumocyte necrosis. It is inferred that human diffuse alveolar damage develops in the same way.

INTRODUCTION

Increasing numbers of substances, environmental and therapeutic, are being found to be injurious to the human lung (Rosenow 1972). Bleomycin used in the treatment of certain malignant neoplasms can have toxic pulmonary side effects (Bedrossian et al. 1973). The toxic lung changes in man have been variously described as interstitial pneumonia, interstitial pneumonitis, interstitial pulmonary fibrosis and diffuse alveolar damage. This varying terminology reflects the differing stages of the lesion at which it has been examined. The purpose of this paper is to describe the pathology of two cases of pulmonary bleomycin toxicity in man and to compare this damage with previously reported changes in the lungs of experimental animals (Adamson & Bowden 1974; Aso et al. 1976; Jones & Reeve 1978), in order to understand the nature and evolution of the lung injury in man.

Case Reports

Case 1

In 1955 this patient aged 73 years had a radical vulvectomy for a well differentiated squamous cell carcinoma. She had local skin recurrences in 1962, 1964, 1972, 1974 and 1975, all treated by local excision. In July 1975 she was admitted to hospital for severe lower abdominal pain and urinary incontinence. Further local recurrence with the presence of intraperitoneal secondaries was suspected. She was given intramuscular bleomycin (15 mg twice weekly) which produced some improvement in the local recurrences, but she continued to have severe abdominal pain and urinary incontinence. A chest radiograph taken 18 weeks after bleomycin treatment was started showed nodular shadowing throughout the lung fields, most marked at the bases. Bleomycin was discontinued, a total of 660 mg of the drug having been given. Subsequently she developed congestive cardiac failure and died on 19 January 1976. Autopsy revealed signs of congestive cardiac failure; there was no evidence of recurrent carcinoma either in the vulval region or within the abdomen.

Case 2

A man aged 71 years developed a squamous cell carcinoma of the glans penis with a metastasis in the dermis and subcutaneous tissue of the left inguinal region. A partial amputation of the penis with excision of the inguinal mass and the overlying skin was carried out. Pre- and postoperatively he was given intravenous bleomycin (15 mg twice weekly; total dose 150 mg) for 5 weeks and then discharged from hospital.

About 8 weeks later he became breathless on exertion; this became progressively more severe and on 1 August he was re-admitted to hospital. A chest radiograph showed abnormal shadowing throughout the lung fields consisting of a combination of micronodular and linear markings, most marked in the perihilar and the mid and lower lung fields. Chest radiographs taken in 1957 and immediately before bleomycin therapy had shown no abnormality. On 8 August the blood pH was 7.45, $P\text{co}_2$ was 35 mmHg and $P\text{o}_2$ 55 mmHg. Pulmonary function tests were those of a restrictive pulmonary disorder. He was given prednisolone 45 mg/day for 18 days, with subsequent improvement in the pulmonary function tests; the prednisolone was then reduced to 15 mg/day. On 31 August he complained of abdominal pain which progressively became more severe. A provisional diagnosis of peritonitis was made, but before laparotomy the patient died. The autopsy showed perforation of an acute gastric ulcer with peritonitis.

PULMONARY PATHOLOGY

The descriptions apply to formaldehyde inflated left lungs in both cases.

Case 1

There was extremely fine diffuse fibrosis at the bases of the left upper lobe and left lower lobe but this had not progressed to a honeycomb pattern. There were a few small thromboemboli in the left upper lobe. The histological changes were variable, ranging from the normal to established interstitial fibrosis. The various changes could be arranged in a sequence, which may represent the progression of the lesion.

In the most recent lesions the alveolar pattern was obscured by areas of intra-alveolar haemorrhage, oedema and fibrin deposition with widening of the alveolar walls resulting from interstitial oedema and lymphocyte infiltration (Fig. 1). The normal lung pattern was further obscured by the intra-alveolar accumulation of a variable number of foamy macrophages. Some alveoli were lined by large pleomorphic cells, with plentiful cytoplasm and prominent central nuclei. These cells occurred either singly or as irregular rows (Fig. 2). (These were sometimes detached from the alveolar walls due to post-mortem change.)

In older lesions there was increased collagen which was localized mainly in the alveolar walls, but there was also increased intra-alveolar collagen, the incorporation of which into already distorted alveolar walls produced further disorganization of the lung architecture.

In the inactive areas there was established interstitial fibrosis with some microcyst formation, where the air spaces were lined by regular cuboidal cells (*cf.* Fig. 3). There were scanty foci of squamous metaplasia at the junction of small bronchi and alveoli.

Case 2

The pleural surface of the inflated left lung showed no abnormality. There was diffuse,

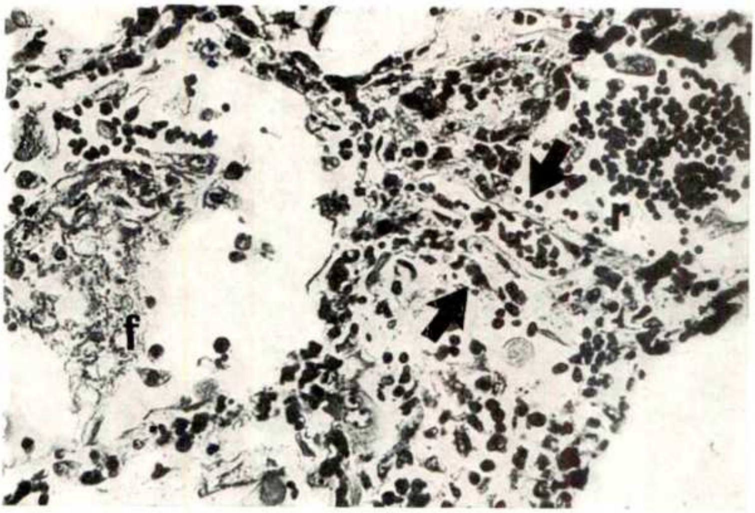

Fig. 1. The early stage of diffuse alveolar damage. There is considerable disorganization of the alveolar pattern resulting from intra-alveolar accumulation of fibrin (f), red blood cells (r) and macrophages. The alveolar walls are widened (arrows) and difficult to distinguish. Masson's trichrome × 300

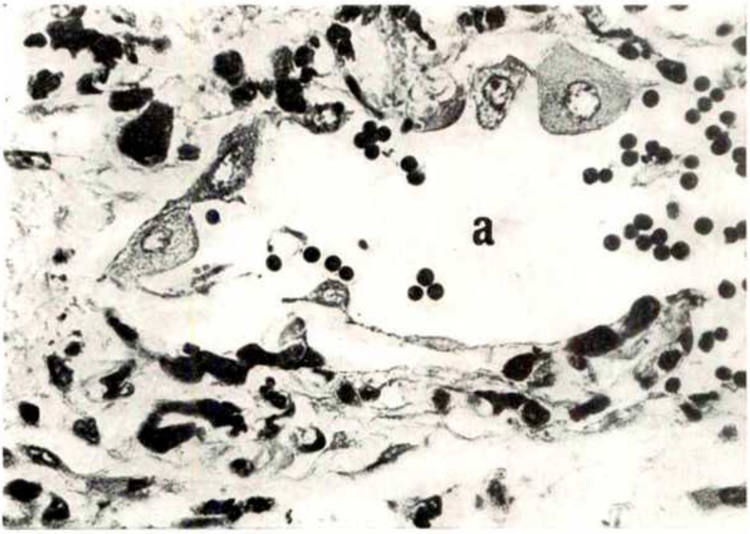

Fig. 2. An air space (a) is partly lined by type II pneumocytes with plentiful cytoplasm and vesicular nuclei. The presence of these cells indicates previous type I pneumocyte necrosis. Masson's trichrome × 510

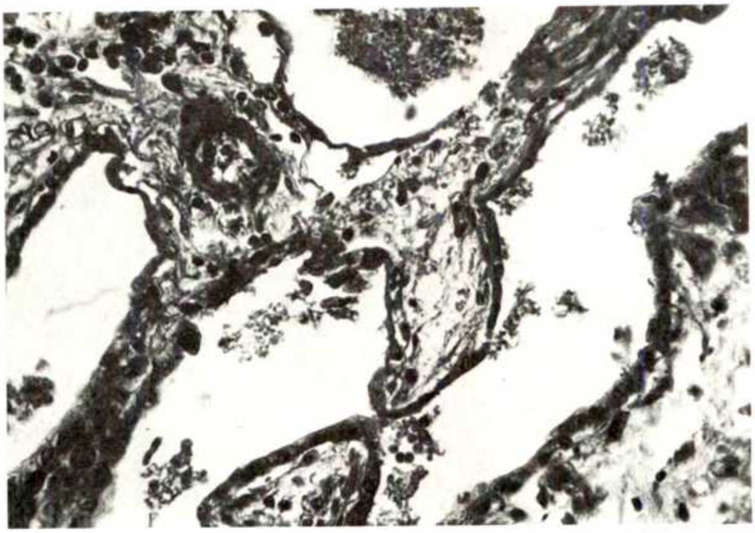

Fig. 3. Interstitial fibrosis with the distorted air spaces lined by cuboidal cells. Masson's trichrome × 300

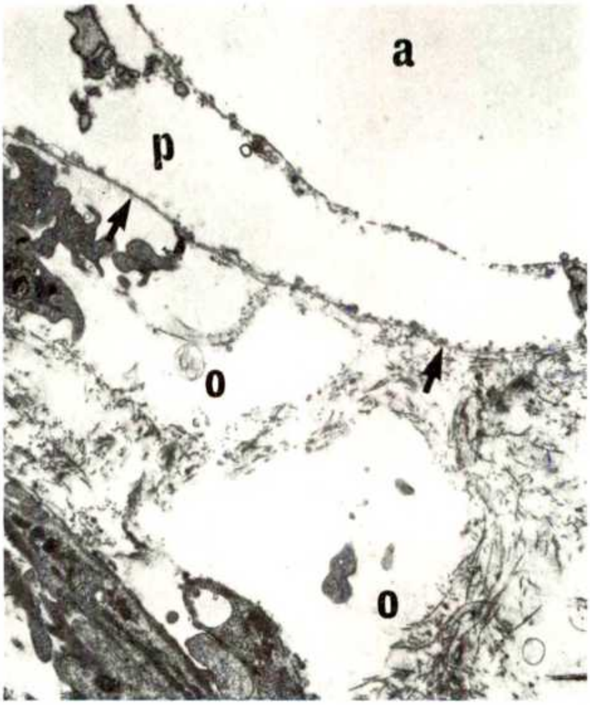

Fig. 4. Electronmicrograph of bleomycin induced pulmonary damage in the mouse. Part of an oedematous alveolar wall (o) is covered by a necrotic type I pneumocyte (p). The alveolar basement membrane (arrows) is intact. Bleomycin produces vascular damage with resulting oedema and type I pneumocyte necrosis. Alveolus (a). × 6250

but non-uniform fibrosis, most conspicuous at the apex and base of the left upper lobe. There was also fibrosis in the mid-zone of the left lower lobe associated with recent intra-alveolar haemorrhage. Numerous small thromboemboli were present in the left upper lobe.

The microscopic findings were, in general, similar to Case 1, except that the more active lesions were less apparent and there was more established fibrosis with larger cystic spaces lined by regular cuboidal cells (Fig. 3).

In neither case were typical hyaline membranes seen, although there was much intra-alveolar fibrin deposition.

DISCUSSION

Diffuse alveolar wall damage is probably the commonest form of drug induced pulmonary disease (Rosenow 1972; Davies 1969). The damage may be of the hypersensitivity type, of which nitrofurantoin is the best documented cause (Hailey et al. 1969) or it may be a dose-related non-hypersensitivity reaction as in the case of bleomycin.

In human bleomycin lung injury the damage is confined to the lung periphery and in particular to the alveoli. The alveolar walls are damaged with the production oedema; there is fibrin deposition, interstitial round cell infiltration with subsequent intra-alveolar and alveolar wall fibrosis. Ultrastructural studies of the human lesions have demonstrated type I pneumocyte necrosis and reactive type II pneumocyte hyperplasia (Bedrossian et al. 1973). Experimental studies of bleomycin induced lung damage in mice have shown conclusively that the drug acts at two sites, it damages the pulmonary vasculature with subsequent oedema and it produces extensive type I pneumocyte necrosis (Adamson & Bowden 1974; Aso et al. 1976; Jones & Reeve 1978) (Fig. 4). All subsequent changes are a consequence of these two actions. All three studies showed that type I pneumocyte necrosis was followed by type II pneumocyte hyperplasia and that there was probably hyperplasia of cells of the small bronchi with subsequent peripheral migration of the cells into the damaged alveoli.

The changes in these two patients with bleomycin lung injury can now be interpreted in the light of the available experimental evidence. The initial acute histopathological changes are the result of direct action of bleomycin on the small pulmonary vessels resulting in widespread oedema, intra-alveolar haemorrhage and fibrin deposition. As no ultrastructural studies of these two lungs were carried out type I pneumocyte necrosis can be inferred only from the hyperplasia of the alveolar type II pneumocyte, as this signifies repair of the alveolar epithelium. In man bronchial squamous metaplasia occurs and, although there is no exact counterpart in the mouse, there is hyperplasia of the bronchial epithelium. These changes are the result of organization and repair phenomena which are common to many forms of alveolar damage.

Comparison of the experimental and human lung changes indicate the lesions to be similar, yet these changes are not specific to bleomycin, for agents such as oxygen (Adamson et al. 1970) and paraquat (Vijeyaratnam & Corrin 1971) produce a similar form of lung damage. Only limited studies have been carried out on the busulphan lung (Heard & Cook 1968; Littler et al. 1969; Kirschener & Esterly 1971), but the findings can be interpreted as being similar to bleomycin, oxygen and paraquat lung damage. The type I pneumocyte and the small pulmonary blood vessels appear to be the lung components most susceptible to damage, and consequently many diverse injurious agents produce a similar pulmonary reaction, which may be termed diffuse alveolar damage, as suggested by Luna et al. (1972) and Katzenstein et al. (1976).

A partial explanation for the toxic action of bleomycin on the lung is that the drug is selectively concentrated there; high levels are also achieved in the skin, which is also subject to toxic changes. The nature of the anti-tumour action of bleomycin is unknown. Although it is known to prevent DNA synthesis in neoplasms (Kunimoto et al. 1967), it remains to be shown whether this action has any relevance to its pulmonary effect. As yet ultrastructural studies have shown only its sites of action but not its mechanisms of action.

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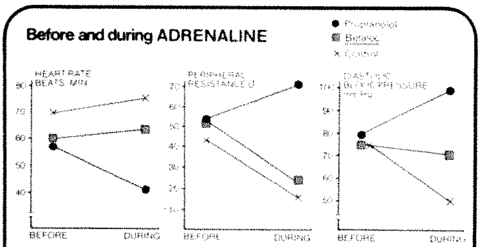

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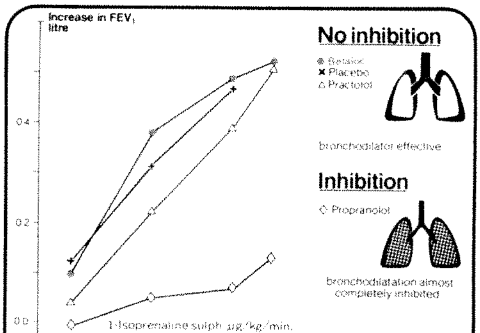

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1 Johnsson G. (1975), *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68. University of Gothenburg, Sweden.

2 Svedmyr *et al*, Clinical Report (1975), University of Gothenburg, Sweden.

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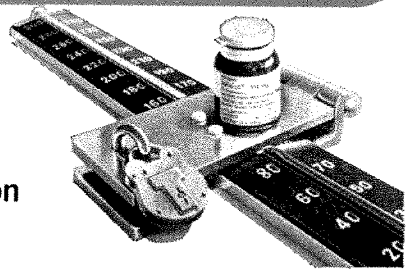

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Br. J. Dis. Chest (1978) 72, 327

THE EFFECTS OF ORAL PROPRANOLOL AND METOPROLOL ON LUNG FUNCTION AND EXERCISE PERFORMANCE IN CHRONIC AIRWAYS OBSTRUCTION

C. R. McGavin* and Isobel P. Williams

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Summary

Fifteen men with chronic airways obstruction recieved a test dose of propranol 20 mg orally. Six developed increased breathlessness. Nine who tolerated the test dose received metoprolol (100 mg) and propranolol (80 mg) on different days in a randomized double-blind fashion. Changes in resting and excercise heart rate, spirometry and exercise tolerance were measured 1 and 6 hours later. The drugs had similar effects on heart rate. Propranolol, but not metoprolol, caused significant reduction in forced expiratory volume in one second (FEV_1) and peak expiratory flow rate. Neither drug produced significant changes in forced vital capacity (FVC) or excercise performance in the group as a whole, although the range of changes was wide. Despite considerable reduction in FEV_1 and FVC in some individuals, most reported no increase in symptoms.

Changes in exercise tolerance at 1 hour correlated significantly with changes in FVC but not with those in FEV_1. It is proposed that changes in FEV_1, though of pharmacological interest, may be less relevant clinically than changes in FVC.

INTRODUCTION

Valuable information about the pharmacology of β-adrenergic blocking drugs has been obtained by studying their effects on respiratory function tests in asthmatics (Johnsson et al. 1975). Thiringer and Svedmyr (1976) have shown that metoprolol produces less reduction in forced expiratory volume in one second (FEV_1) than propranolol and that this effect is more readily reversed by isoprenaline. They conclude that metoprolol has β_1 receptor selectivity and can be used in asthmatics provided it is combined with a β_2 receptor stimulant. β-blockade might be expected to have a less deleterious effect on respiratory function in patients with relatively irreversible airways obstruction than in the labile airways obstruction of episodic asthma. Furthermore, clinical problems such as angina pectoris and hypertension for which β-blockade might be indicated are more likely to occur in patients with chronic obstructive bronchitis. This study was designed to compare the effect of oral metoprolol and propranolol on airways function tests in subjects with chronic airways obstruction, and to assess whether changes in exercise performance correlate with those in respiratory function tests.

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Patients and Methods

The subjects were men under the age of 70 years with breathlessness due to airways obstruction, incompletely reversible with bronchodilator drugs. No patient had an FEV_1/FVC ratio of more than 52% and the mean was 38%. The mean FEV_1 as a percentage of predicted values was 40%, range 18–76%. All the subjects were smokers or ex-smokers, all were in sinus rhythm and in a stable state of their disease and none had angina pectoris or intermittent claudication.

FEV_1 and FVC were measured on a vitalograph apparatus (Drew & Hughes 1969); the best of three technically satisfactory readings was taken and expressed at body temperature and pressure, saturated. The Wright Peak Flow Meter was used to measure peak expiratory flow rate (PEFR). Mixed venous Pco_2 ($P\bar{v}co_2$) was estimated by the re-breathing technique of Campbell and Howell (1962). Excercise tolerance was measured by a 12-min walking test (McGavin et al. 1976*a*). In this test the subject walked as far as he could along a level corridor in 12 min, regardless of whether he had to stop for breath or not. The total distance covered was expressed in metres.

Tests were carried out on three days, starting at approximately the same time of day. The subjects abstained from bronchodilators for at least 10 hours and had only a light breakfast before the tests. The first day was a preliminary visit. The nature of the study was explained and informed consent obtained. Each subject was warned that the drug might aggravate his breathlessness, but that this could be reversed by medication and that he could stop the tests if he wished. He underwent an assessment consisting of a cardiorespiratory history, physical examination, electrocardiography and chest radiography. Measurements of FEV_1, FVC, $P\bar{v}co_2$ and 12-min walking distance (12-MD) were made. If these were satisfactory, a test dose of propranolol 20 mg was given orally. The first few subjects were observed in the laboratory for 90 min and then allowed home. However, after some subjects reported breathlessness coming on hours later, all subsequent subjects were admitted for 24 hours to a medical ward.

Those who tolerated the test dose attended on two further days separated by an interval of 24 or 48 hours. The order of tests was the same on the two days. Resting pulse rate, FEV_1, FVC and PEFR were measured. The subject carried out the walking test and his pulse rate was counted immediately at the end of the exercise period. He then received a coded tablet containing either metoprolol 100 mg or propranolol 80 mg in a randomized double-blind cross-over fashion. The tests were repeated 1 and 6 hours later, and in the interim hourly observations of PEFR were made. After the last test the subject was asked whether he had experienced considerable, slight or no change in his breathing, and he was allowed home 20 min later.

RESULTS

The preliminary day

Fifteen men received the test dose of propranolol. Six experienced worsening symptoms such that the doctor supervising thought it unwise to proceed to larger doses and these subjects were withdrawn from the study. The symptoms consisted of increasing breathlessness or wheeze, coming on 4–12 hours later. In no case was the reaction severe enough to require parenteral administration of β-agonists. No problems arose due to bradycardia or claudication. Data concerning the six who were withdrawn (Group A) and the remainder who tolerated the test dose (Group B) are given in Table I. There are no significant differences between the groups in age, $P\bar{v}co_2$, FEV_1 or FVC. Two in Group A had clinical features compatible with an asthmatic component (childhood wheeze and positive prick tests) compared with one in Group B (aggravation of symptoms during the pollen season). Three in Group A were taking corticosteroid drugs or disodium cromoglycate, compared with one in Group B.

The double-blind study

Six of the nine subjects received propranolol before metoprolol. There were no signifi-

Table I. Basic data on all subjects

	Age	FEV_1	*FVC*	$P\bar{v}_{CO_2}$	*Medication*[*]	*Asthmatic features*
Group A						
	64	0.70	2.25	53		
	66	0.85	2.10	48	D	+
	63	1.00	2.97	60		
	64	1.55	3.42	44	S	
	62	0.50	1.65	46	S	+
	52	1.35	3.00	49	S	
Mean	62	0.98	2.57	50		
SD	5	0.41	0.67	6		
Group B						
	66	0.55	1.50	—	S	
	60	0.65	2.50	68		
	61	1.83	4.60	43		
	66	1.25	3.40	43		
	62	1.35	2.60	57		+
	64	0.72	2.35	55		
	67	1.65	3.43	41		
	55	1.08	2.43	47		
	65	1.11	2.75	—		
Mean	63	1.15	3.04	50		
SD	4	0.43	0.99	10		

[*] D = sodium cromoglycate; S = corticosteroids.

Table II. Measurements before and after β-blocking drugs

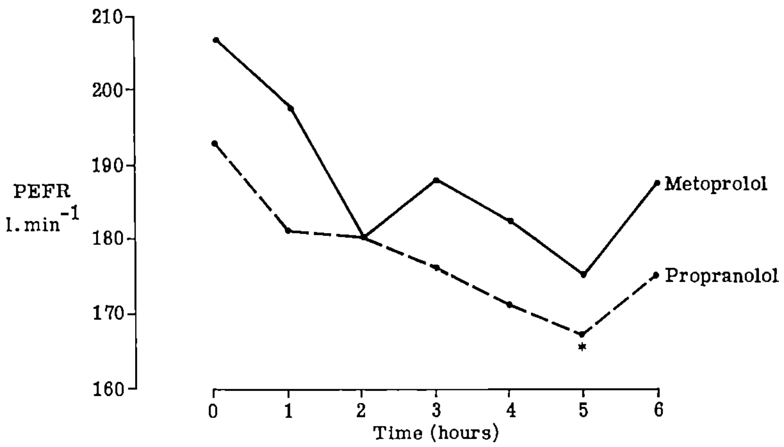
Measurement	*Drug*	*Time*		
		0($n=9$)	1 hour ($n=9$)	6 hours ($n=7$)
Resting pulse	Propranolol	75 ± 11	58 ± 10†	58 ± 5†
	Metoprolol	79 ± 15	61 ± 9*	60 ± 10†
Exercise pulse	Propranolol	106 ± 14	79 ± 9*	81 ± 6†
	Metoprolol	110 ± 22	79 ± 11*	78 ± 7†
FEV_1 (litres)	Propranolol	1.25 ± 0.49	1.10 ± 0.48†	1.10 ± 0.45†
	Metoprolol	1.15 ± 0.43	1.13 ± 0.53	1.19 ± 0.38
FVC (litres)	Propranolol	3.06 ± 1.04	2.93 ± 1.04	2.95 ± 1.29
	Metoprolol	3.04 ± 0.99	3.11 ± 1.2	2.81 ± 1.25
12-MD (m)	Propranolol	1058 ± 255	1006 ± 314	1158 ± 162
	Metoprolol	1059 ± 314	1029 ± 307	1154 ± 199

* $P < 0.001$, † $P < 0.01$, ‡ $P < 0.05$, compared by a paired *t*-test with the pre-treatment value. Mean values are given with one standard deviation.

cant differences between the values of FEV$_1$, FVC, PEFR, 12-MD and pulse rate before the administration of the two drugs. Two subjects did not undergo the tests at six hours. The results are summarized in Table II.

Resting and exercise pulse rates were significantly lower than the pre-treatment value after both drugs, and there was no difference between the effect of the drugs, from which it may be inferred that they achieved similar cardiac β-blockade. The FEV$_1$ was reduced by a mean of 0.15 litres at 1 hour and 0.27 litres at 6 hours after propranolol, both figures being significant at the 5% level. The mean reductions after metoprolol of 0.02 litres at 1 hour and 0.03 litres at 6 hours were not significant. The FVC was not reduced significantly by either drug; the mean changes at 1 and 6 hours after propranolol were −0.13 litres and −0.19 litres, and after metoprolol they were +0.07 litres and −0.33 litres respectively. The 12-MD was not affected significantly by either drug; the mean and percentage reductions at 1 and 6 hours after propranolol were 52 m (4.9%) and 2 m (0.1%), and after metoprolol they were 29 m (2.7%) and 32 m (2.7%). The differences in the means from 0 to 6 hours differ from those calculated from the data in Table II because the mean at time 0 in Table II is derived from data on nine and not seven subjects.

Changes in PEFR are shown in Fig. 1. Although falls in mean PEFR were observed after both drugs, the only value reaching significance at the 5% level was that at 5 hours after propranolol.



*Significant change from zero time p=< 0. 05

Fig. 1. Changes in mean PEFR

As regards symptoms, only one subject—the man with the lowest initial FVC—reported a major change in his breathing after the bigger dose of β-blocker. He stated that propranolol caused a considerable deterioration but metoprolol produced no change. At 1 hour the percentage reductions in his FEV$_1$ were 23% (propranolol) and 13% (metoprolol). The equivalent figures for FVC were 33% and 4%, and for 12-MD were 31% and 15%. After the drug administrations where the subjects reported no change in symptoms at 6 hours, the range of changes in spirometric measurements was wide. For FEV$_1$, it was −35 to +12% (mean −14 ± SD 14%) and for FVC it was −38 to +19% (mean −7 ± SD 15%).

A highly significant linear correlation existed between changes in FVC and in 12-MD at 1 hour in the 18 observations made on nine subjects. This was true whether the changes were expressed in absolute values ($r = 0.71$, $P = < 0.001$) or as percentage change from the initial value ($r = 0.65$, $P = < 0.001$). The correlation was no longer observed at 6 hours in the seven subjects. There was no correlation between changes in FEV_1 and 12-MD at any time.

DISCUSSION

At the preliminary visit, six subjects became more breathless after 20 mg propranolol. This demonstrates the inadvisability of giving this drug to patients with airways obstruction except under close medical observation lasting at least 6 and preferably 24 hours. It also demonstrates the importance of the sympathetic drive to the bronchial smooth muscle in these patients under basal conditions. The higher incidence of asthmatic features in group A may be relevant.

The results of the double-blind study support the pharmacological concept that metoprolol is relatively β_1 ('cardio-') selective when compared with propranolol. The oral route was used in order to mimic clinical practice and because the intravenous route avoids the first pass metabolism of the drug by the liver (McDevitt et al. 1976). At the doses used the drugs had indistinguishable effects on resting and exercise heart rates. Propranolol reduced FEV_1 and PEFR significantly, but metoprolol did not. We found the reduction in PEFR maximal at 5 hours after both drugs, although a significant drop in FEV_1 had occurred 1 hour after propranolol.

Symptoms often correlate poorly with spirometric measurements in chronic airways obstruction, and it is not surprising to observe acute changes in FEV_1 and FVC without aggravation of symptoms even when the subjects are stressed by exercise. Despite lack of statistically significant changes in FVC and 12-MD, change in FVC correlated well with change in exercise performance within patients at 1 hour. Observations on 105 patients with airways obstruction over a wide range of severity have shown that walking distance correlates better with FVC ($r = 0.48$) than with FEV_1 ($r = 0.38$) (McGavin 1977). However, no correlation was found between increases in walking distance and in FEV_1 or FVC following the administration of inhaled bronchodilators (McGavin et al. 1976*b*).

It is suggested that the airways may be considered in two groups according to calibre. FEV_1 and PEFR are probably largely governed by performance of the larger airways (> 2 mm diameter) and wheeze is generated by oscillations in these airways. Narrowing and obliteration of the smaller airways occurs early in chronic obstructive diseases but does not produce wheeze. Tests of disease in the small airways require sophisticated apparatus and are a matter of controversy. It may be that the FEV_1 and PEFR are useful indicators of pharmacologically mediated events in the larger airways but that the FVC can reflect changes in small airways (Green 1977). Since FVC correlated well with excercise performance it may be that this test, and by implication the small airways, are of greater clinical importance. When assessing the clinical effect of a drug acting on bronchial smooth muscle, perhaps one should pay attention to changes in exercise performance, symptoms and FVC rather than drawing conclusions from the FEV_1 and PEFR alone.

The design of this study does not allow conclusions to be drawn about the feasibility of giving a combination of metoprolol and a β_2 agonist to patients with chronic airways obstruction, but this would be an important point in clinical practice.

ACKNOWLEDGEMENTS

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THE MEASUREMENT OF VITAL CAPACITY AND MINUTE VOLUME WITH THE WRIGHT RESPIROMETER

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The Wright Respirometer (Wright 1955) was originally intended for the measurement of exercise ventilation and so had two dials, one reading to 100 litres and the other to 1 litre. The reading of volumes of a few litres has always been difficult with a 100:1 ratio between the two dials because it is easy to make a mistake of 1 litre when reading to fractions of a litre. Although it is known (Nunn & Ezi-Ashi 1962) that the respirometer can measure resting minute volumes accurately, in practive it has been used mainly for tidal volumes, and the possibility of measuring vital capacity (VC) has not been considered because of the difficulty of reading the dials.

A new model of the Wright Respirometer has now become available with a 10:1 ratio between the dials , so it seemed worthwhile to determine the accuracy with which the instrument could measure vital capacity.

METHOD

A prototype Wright Respirometer with 10:1 dials was connected in series with a Vitalograph dry spirometer, the accuracy of which was checked with a calibrated water spirometer; it was found to have a maximum error of 2%.

There were 84 subjects of both sexes, age range 14–70 years, including some smokers. Fourteen had chronic bronchitis, 38 asthma and 32 no chest disease. Each subject was asked to deliver three vital capacity breaths without forcing. The rate of delivery varied and some subjects delivered forced vital capacities, which can damage the respirometer, but fortunately no damage resulted. The Vitalograph and respirometer readings were not corrected to body temperture and pressure (BTPS).

RESULTS

The means of the three readings of VC in each of the 84 subjects as measured by the two instruments are plotted in Fig. 1. The correlation between the two means is very good ($r = 0.995$) but the Wright Respirometer reads consistently about 9% higher than the Vitalograph.

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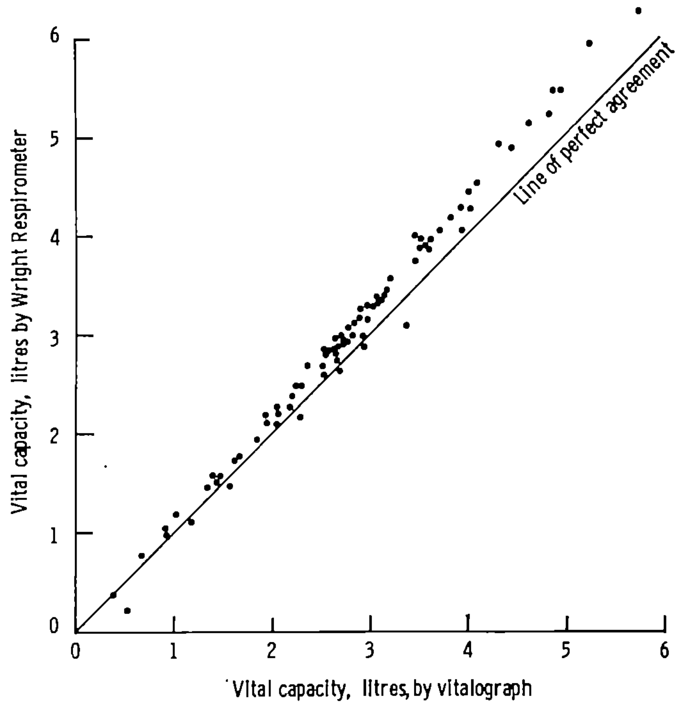

Fig. 1. Correlation between vital capacities measured with Wright Respirometer and Vitalograph. For details see text

DISCUSSION

The closeness of the correlation between the two instruments is somewhat surprising as the Wright Respirometer does not register flows below 2 litres/min, causing serious undereading and variation of calibration factor at low flow rates (Wright 1958). Although the tail-end of a VC may be delivered at a very low flow rate, the volume contained in the tail is a small fraction of the whole and so has comparatively little effect. Most of the volume is delivered at a fairly high flow rate, when the calibration factor is relatively constant, so that the very varied rates of delivery of VC did not produce much variation. Even a defective respirometer with a slip of 3 litres/min was found to give results indistinguishable from those given by a good instrument.

The effect of the temperature and humidity of the air passing through each instrument is complicated. The respirometer has a relatively low thermal capacity and was close to the mouth so that the air temperature varied from that of the room to that of end-expired air (about 35°C) saturated with water vapour. The Vitalograph, on the other hand, measured air saturated at approximately room temperature (ATPS) and this difference could account for much of the observed constant error and some of the variation between the instruments. Since the BTPS value is about 10% greater than the ATPS, the reading from the Wright Respirometer will be close to the BTPS value.

It is therfore suggested that, with the new dial presentation, the Wright Respirometer is suitable for the measurement of vital capacity as well as minute volume in clinical practice.

ACKNOWLEDGEMENTS

We are indebted to Dr J. F. Nunn for suggesting the project and to the Department of Medical Illustration of the Clinical Research Centre for the illustration. The work formed part of a Clinical Project carried out by A.P.D. and G.F.N. while final year students at St Mary's Hospital, Paddington.

The Mark 14 Wright Respirometer is available from the British Oxygen Co. and we are grateful to them for the loan of the prototype.

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PEDUNCULATED CAPILLARY HAEMANGIOMA OF THE BRONCHUS

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Summary

The case of a patient with a pedunculated capillary haemangioma of the bronchus is described and discussed.

Introduction

Capillary haemangioma of the bronchus must be a very rare lesion; we have been unable to find a single case in the English literature of the last 20 years. Cases of a morphologically similar tumour, haemangioma of the lung, have however been documented. In 1968 Mori reviewed 23 cases in the world literature and presented one further case; discounting arteriovenous fistulae as separate discrete entities, the cases which he discusses are all solid, spherical intrapulmonary haemangiomas. These he classifies into haemangiomas of alveolar capillary origin (haemangioblastomas, vascular endotheliomas, capillary haemangiomas and sclerosing haemangiomas), and haemangiomas arising from the pericytes of Zimmermann. Of the 24 cases, four are capillary haemangiomas and one is a hamartomatous haemangioma of capillaries; no mention is made of capillary haemangioma of the bronchus.

The first case of pulmonary haemangioma arising from alveolar capillaries was described in 1923 by De Lange and De Vries Robles in a 2-month-old male infant with three separate such lesions in the lungs. The hamartomatous haemangioma of capillaries was in a 14-day-old female child with 5 discrete tumours in the lungs (Rankl 1942). The only 2 cases of capillary haemangioma of lung in the English literature presented clinically with haemoptysis in adult females. Chest radiographs showed 'a solitary spherical intra-pulmonary non-hilar density ("coin lesion")' in each case (Goorwitch & Madoff 1955; Magri et al. 1957). A similar case is recorded in the Japanese literature (Noda et al. 1966).

Haemangiomata of the upper respiratory tract are relatively more common, though still rare. Littler (1963) describes a case of asphyxiation due to an obstructing haemangioma of the trachea in an infant, and cites references to subglottic haemangiomata of the larynx and trachea.

If capillary haemangiomas of the upper respiratory tract or of alveolar capillary endothelial origin are rare, then a capillary haemangioma of bronchus could be unique; furthermore, the case which we describe is of interest not only for its extreme rarity, but also because of the unusual (and initially confusing) changing radiological appearances which it produced.

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Case Report

A 67-year-old housewife who had previously been in good health was admitted to hospital as an emergency in November, 1975, complaining of three episodes in 3 days of severe, constricting, central chest pain radiating to the left side and to the neck, each attack lasting about 1 hour, commencing suddenly on turning to the left side, and being so severe that the patient was unable to lie still. Slight dyspnoea on climbing stairs followed the first attack of pain and persisted for several days. Expectoration of a small quantity of blood-stained sputum 3–4 hours after the first chest pain, continued intermittently for 5 days. She had smoked 10–20 cigarettes per day for many years. A previous chest radiograph taken in 1971 was reported as normal.

The patient was treated initially with antibiotics by her general practitioner (for a presumed chest infection), but when symptoms persisted he arranged for her urgent admission to hospital. She was there found on examination to have diminished breath sounds and vocal fremitus at the left base, and a first hospital diagnosis of pulmonary embolism was made. However, postero-anterior and left lateral chest radiographs showed collapse/consolidation of the left *upper* lobe and lingula (Fig. 1), and a penetrated postero-anterior radiograph demonstrated a left hilar mass (Fig. 2). The diagnosis was revised to obstructive pneumonia of the left upper lobe and lingula secondary to bronchogenic carcinoma. Ampicillin was prescribed, but haemoptysis persisted and the patient experienced a further episode of chest pain.

Hilar tomography on the day following admission did not confirm the hilar mass (Fig. 3). The left upper lobe bronchus and lingular branch appeared patent, but rather surprisingly the left lower lobe bronchus could not be demonstrated. The radiologist reporting the tomograms commented 'I do not know quite where this leaves us'.

Fibre-optic bronchoscopy a few days later showed the larynx, trachea, carina and right bronchial tree to be normal. The left upper lobe bronchus including the lingular segmental branch was normal; the left lower lobe bronchus was obstructed with white fibrinous tissue of rather strange

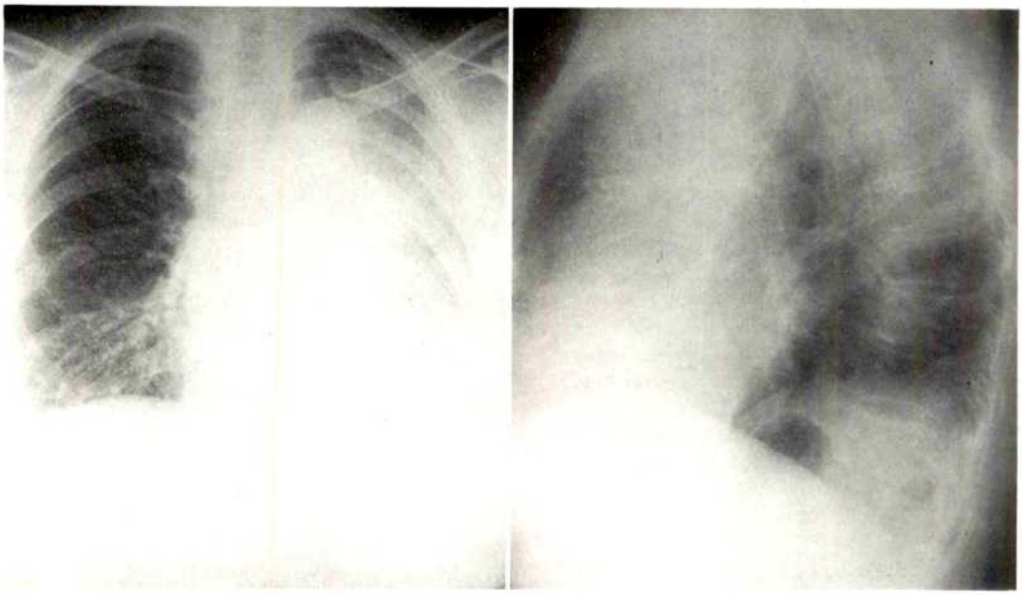

Fig. 1. Postero-anterior and left lateral chest radiographs on admission showing collapse and consolidation of the left upper lobe and lingula

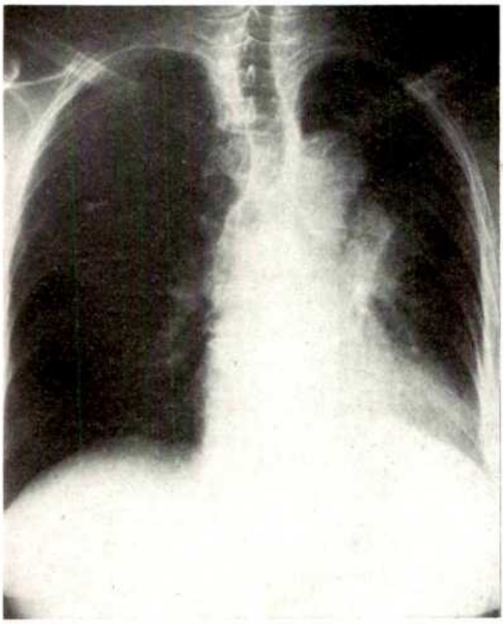

Fig. 2. Penetrated postero-anterior chest radiograph on admission showing a left hilar mass

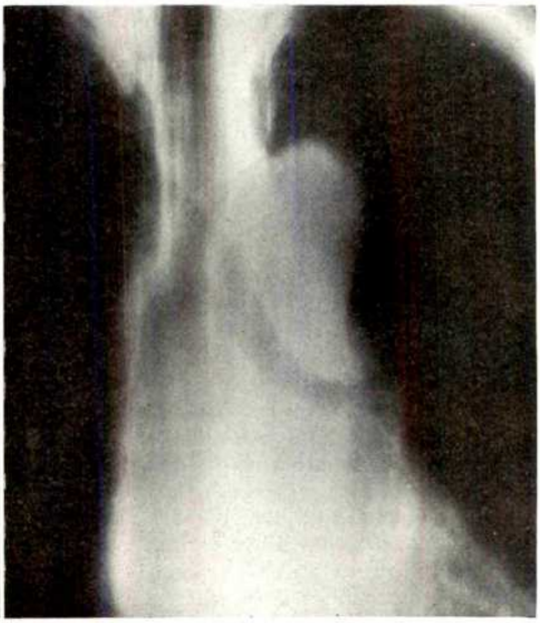

Fig. 3. Hilar tomography one day later showing disappearance of the left hilar mass, patent left upper lobe and lingular bronchi, and occluded left lower lobe bronchus

appearance projecting upwards into the main bronchus. Very tenacious blood-stained sputum was aspirated and two biopsies were taken from what was thought to be necrotic tumour. It was concluded that the appearance was that of a carcinoma of the lower lobe bronchus, but histology showed normal bronchial mucosa and some necrotic debris. Six sputum samples examined cytologically up to this time proved negative for malignant cells.

Two weeks after the original onset of symptoms the patient was improved and a chest radiograph showed resolution of the left upper lobe signs, and a vascular pattern consistent with a degree of collapse of the left lower lobe. This appearance was unchanged one week later, and a repeat bronchoscopy showed the left lower lobe bronchus to be blocked with old fibrin and blood clot, some of which was removed in the form of a worm-like cast. There seemed to be some stenosis of the lower lobe bronchus. Two biopsies were reported as fibrinopurulent material and normal bronchial mucosa. A bronchogram showed that the left upper lobe and lingular bronchi were normal; the left lower lobe bronchus demonstrated limited filling, and there was evidence of almost complete collapse of the left lower lobe (Fig. 4). The patient remained clinically well.

A third bronchoscopy was performed after a further 10 days. A small, red, pin-head sized swelling was present in the left main bronchus between the left upper and lower lobe bronchi. The upper lobe and lingular bronchi were again found to be patent, but the lower lobe bronchi looked somewhat narrowed. Excision biopsy of the pin-head sized growth was taken and some haemorrhage occurred after this. Bronchoscopically the differential diagnosis of the lesion was thought to be, small adenoma, angioma or granulation tissue. A second bronchogram performed after bronchoscopy showed filling of the left lower lobe bronchus (Fig. 5). The anterior and lateral basal and apical lower lobe segmental bronchi appeared normal. The posterior basal segmental bronchus was dilated, did not fill completely and contained a number of filling defects thought to represent blood or mucus. There was still some collapse of the lower lobe. The upper lobe and lingular bronchi were of normal appearance.

The excised lesion consisted macroscopically of a single strip of pale tissue, 12 mm in length, with an attached vascular pedunculated lesion no more than 1 mm in diameter. Microscopically

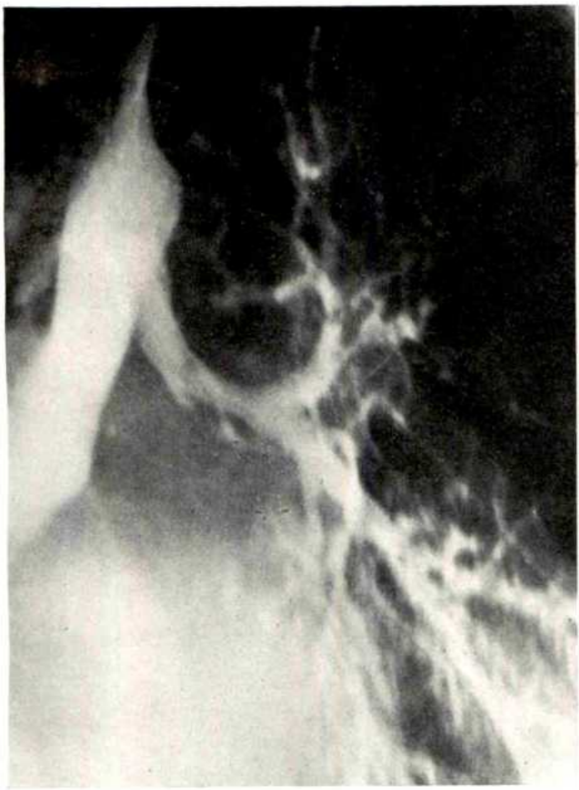

Fig. 4. Left bronchogram at two weeks showing normal left upper lobe and lingular bronchi, failure of filling of left lower lobe bronchus, and left lower lobe collapse

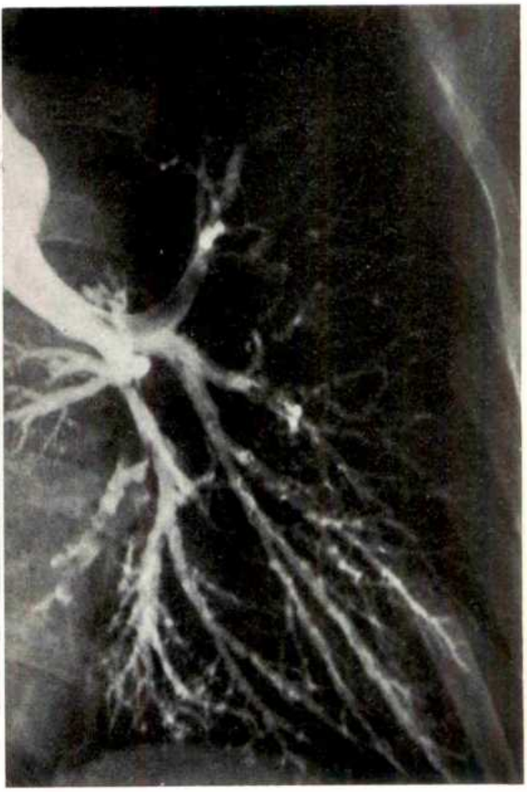

Fig. 5. Second left bronchogram at one month showing filling of left lower lobe bronchus, with incompletely filled dilated posterior basal segmental bronchus containing filling defects, and normal anterior basal, lateral basal and apical lower lobe bronchi

the pedunculated lesion had the features of a capillary haemangioma with a thin-walled vessel within the core, communicating with a somewhat dilated thin-walled vessel in the bronchial submucosa (Figs 6, 7).

The patient was well on subsequent discharge home from hospital. She remained free of symptoms and clinical signs, and chest radiographs have been normal for 8 months. A follow-up bronchoscopy at 4 months after excision of the capillary haemangioma showed no evidence of recurrence and the entire left bronchial tree appeared normal.

DISCUSSION

The unusual, changing radiological features are of interest. The initial radiological appearance of left upper lobe and lingular collapse with a left hilar mass can be attributed to haemorrhage into the left upper lobe and lingular bronchi. Rapid resolution within 24 hours followed expectoration of this local accumulation of thrombus. Subsequent left lower lobe collapse occurred following further haemorrhage into, and occlusion of, the more dependent left lower lobe bronchus, and this was slower to resolve.

Two points merit further discussion of the question why the lesion was not seen

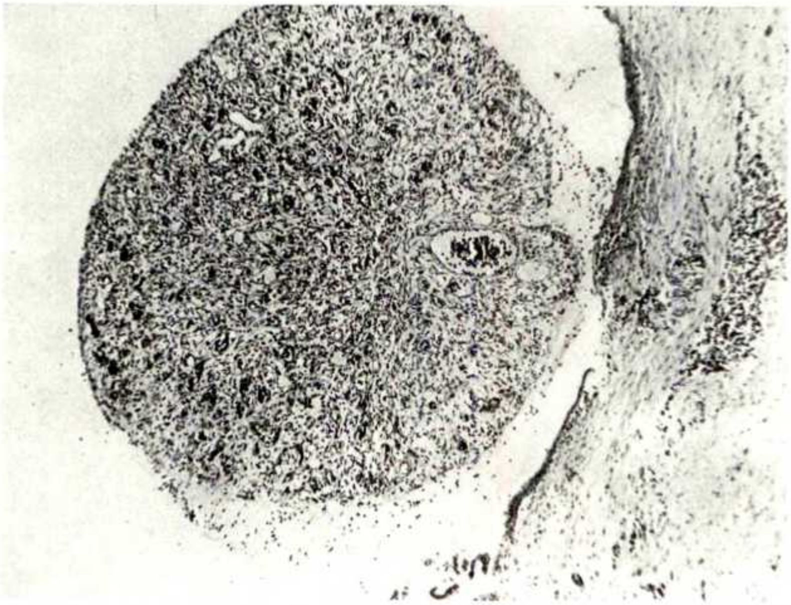

Fig. 6. Low-power view demonstrating the angiomatous nature of the excised lesion. H & E × 70

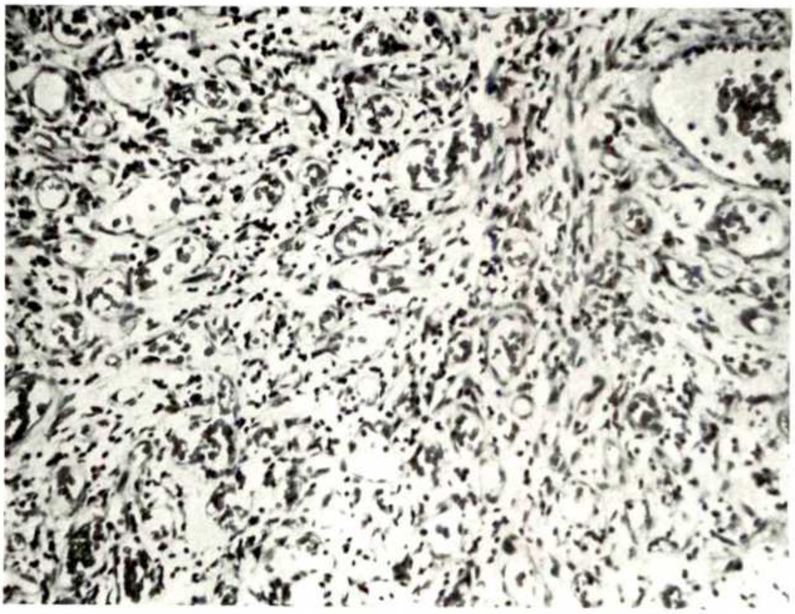

Fig. 7. High-power view. Delicate network of thin-walled vessels with minimal round cell infiltrate in the stroma. H & E × 175

during the first two bronchoscopic examinations. First, it is conceivable that the haemangioma was missed by virtue of its very small size, but possibly no lesion was present at the time of these examinations. Secondly, although the excised lesion was thought to be histologically a capillary haemangioma, it has to be remembered that these can be difficult to distinguish from 'pyogenic granulomas', and a peculiar pyogenic granuloma of recent origin must therefore be considered in the differential diagnosis of the lesion. The origin of a pyogenic granuloma could be suggested as due to trauma during the first or second bronchoscopic examinations, but against this is the fact that the site at which the lesion was ultimately found was not a site of previous biopsy, though trauma from the passage of the bronchoscope itself must still be considered.

Bearing these possibilities in mind, capillary haemangioma is still by far the most likely diagnosis because (*a*) there was no convincing evidence of inflammatory activity of the related bronchial epithelium, and little in the way of any inflammatory component within the lesion itself; and (*b*) a haemangioma would explain the clinical presentation of haemorrhage, at different times, into both parts of the left bronchial tree, whereas a pyogenic granuloma of recent origin would not. Furthermore, no alternative cause of haemorrhage was demonstrated, and finally, the pyogenic granuloma is itself also an exceedingly rare lesion.

This case has both similarities to and differences from those of haemangioma of lung. Mori surmises from his review that haemangiomata of lung (of all types) are more common in women over 30 years of age, and that haemoptysis is a frequent symptom. The three cases of capillary haemangioma arising from alveolar capillary endothelium all presented with haemoptysis, and occurred in a 59-year-old white North American woman (Goorwitch & Madoff 1955), a 30-year-old Argentinian woman (Magri et al. 1957), and a 24-year-old Japanese woman (Noda et al. 1966); bronchoscopy performed twice on the first of these did not contribute to the diagnosis. Each of the three had a solitary 2–2.5 cm coin lesion in the lung and none had any lobar or segmental collapse. This contrasts with the absence of a coin lesion in our case, the almost microscopic pedunculated capillary haemangioma of bronchus producing radiological signs (of lobar collapse and a 'mass' at the hilum) only indirectly as a result of haemorrhage. The bronchial capillary haemangioma was not only diagnosed but also cured by excision at bronchoscopy, whereas the three intrapulmonary haemangiomas required lobar resections to excise the lesion because of inability to exclude neoplasm by other means. The difference in size between alveolar and the bronchial capillary haemangioma could be due purely to differing times of presentation by virtue of different sites of the lesion. Any haemorrhage from an alveolar haemangioma would tend to be limited by surrounding lung tissue without necessarily producing haemoptysis. Mori suggested that haemorrhage from pulmonary haemangiomas may lead to progression of histological change from the original type to that of sclerosing haemangioma.

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We wish to thank Dr J. Henry Jones, Consultant Physician, and Mr I. M. Breckenridge, Consultant Cardiothoracic Surgeon, University Hospital of Wales, for granting permission to record the case report; Mrs Sally Harding for the preparation of the illustrations; and Mrs D. Harding for secretarial assistance.

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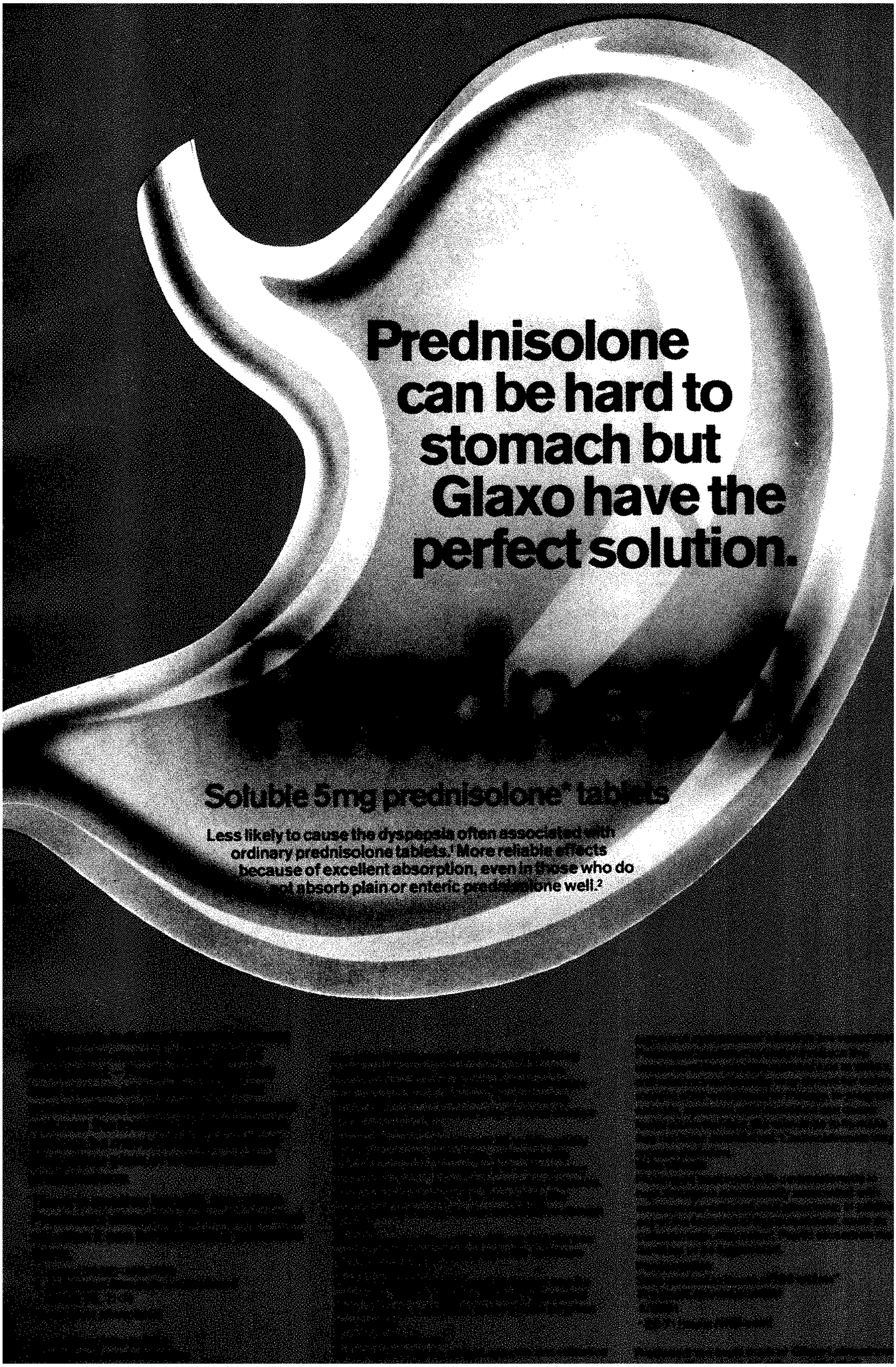
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SARCOIDOSIS MIMICKING MALIGNANCY

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Copthorne Hospital, Shrewsbury, Salop

INTRODUCTION

Sarcoidosis is a multisystem disease which may mimic many others. It is a well recognized but rare cause of pleural effusion (Sharma & Gordonson 1975). It has also been reported as causing ascites. In two of these cases (Porter 1961; Mino et al. 1948) it was associated with portal hypertension and in the third (Halm 1971) with hepatosplenomegaly without portal hypertension. There was no hepatosplenomegaly or evidence of portal hypertension in the case reported here. This patient is of particular interest because she presented clinically as if she suffered from disseminated adenocarcinoma, yet the diagnosis of sarcoidosis was not confirmed until a Kveim test was performed.

Case Report

A 48-year-old woman presented with a dry cough and dyspnoea in December 1975. She had the signs of a right pleural effusion and gross abdominal distension with ascites. A chest radiograph taken then confirmed a large pleural effusion which was subsequently aspirated. After aspiration the chest radiograph showed patchy opacities in both lung fields, mainly in the middle and lower zones. The pleural fluid was a straw-coloured exudate which contained clusters of cells strongly suggestive of an adenocarcinoma.

A tentative diagnosis of ovarian tumour was made. She was referred to a gynaecologist and at laparotomy a large volume of ascitic fluid was aspirated and comment was made that 'the peritoneum was grossly thickened and studded throughout its entire extent by numerous small secondary deposits of malignancy. All the abdominal viscera, gut, liver, uterus and both ovaries were covered with secondary deposits also'. No primary source of tumour was found.

A peritoneal biopsy was taken and histology showed appearances strongly suggestive of a granulomatous peritonitis induced by foreign material. Stains for AAFBs were negative. Cytology of ascitic fluid showed clusters of atypical cells but none identifiable as malignant.

Other investigations at that time included a haemoglobin of 9.5 g/dl, white cell count of 5.5×10^9/litre with a normal differential and an ESR of 32 mm/hour. Urea, electrolytes, calcium, phosphate, total protein, albumin and bilirubin were all normal, but alkaline phosphatase was raised to 456 units/litre (normal <220 units). ASAT was 34 units and electrophoresis showed an increase in γ globulins.

In view of the peritoneal biopsy histology, an alternative diagnosis of sarcoidosis was considered and in March 1976 a scalene node biopsy was performed. This showed sinus histiocytosis with occasional histiocytic granulomas including giant cells. The appearances were not considered typical of sarcoid.

A Kveim test, using fully validated Kveim test suspension, obtained from Standards Laboratories was then performed. A skin nodule was present at 6 weeks. This was biopsied and showed non-caseating tuberculoid granuloma of epithelioid cells and multinucleate giant cells, typical of sarcoidosis.

After aspiration of pleural and ascitic fluid she remained well until December 1976 when ascites had reaccumulated. The chest radiographs at that time showed no further accumulation of pleural fluid but there were still patchy opacities in both lung fields. She was given prednisone

30 mg daily in divided doses. One month later she was symptom-free, and the ascites was clinically less.

DISCUSSION

One feature of this case which led to confusion was the false positive cytology of the pleural fluid. The differentiation of normal mesothelial from malignant cells is very difficult. In one study (Bakalos et al. 1974) it was noted that a definitive distinction between neoplastic and mesothelial cells with the Wright or May–Grünwald–Giemsa staining methods cannot be established. The Papanicolaou method has been found to be more effective in distinguishing normal mesothelial from neoplastic cells, but false positive and negative results still occur. Apart from cell features suggestive of malignancy, normal mesothelial cells may appear in loose clusters and show mitotic activity indistinguishable from that seen in neoplastic cells. This appearance is particularly common in cardiac failure, chronic nephritis, hepatic cirrhosis, pulmonary infarcts and long-standing effusions (Spriggs 1957).

Malignancy was suspected in the case reported here because of the gross ascites, pleural effusion and laparotomy findings. The pleural fluid cytology was thought to be confirmatory, but in fact was subsequently found to be misleading for the reasons discussed above.

It is suggested that when there is diagnostic difficulty in a patient with polyserositis, sarcoidosis should be considered in the differential diagnosis.

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BOOK REVIEWS

Lung Biology in Health and Disease, 3. Bioengineering Aspects of the Lung

John B. West

New York: Marcel Dekker. 1977. Pp. xv + 583. Price SFr 175

This delightful but hopelessly expensive book is the third volume of the series *Lung Biology in Health and Disease* under the general editorship of Claude Lenfant. In it John West has persuaded a series of distinguished (and active) experts to review the physical and mathematical facets of the lung in logical sequence, so: morphology (Weibel and Gil), mechanics (Hoppin and Hildebrandt), flow in the airways (Pedley, Schroter and Sudlow), haemodynamics (Fung and Sobin), gas exchange (West and Wagner), blood gas kinetics (Hill, Power and Longo), and control of ventilation (Grodins and Yamashiro). Text and illustrations are uniformly excellent.

The first chapter by Weibel and Gil, illustrated by beautifully reproduced scanning electron micrographs, describes lung structure, shows how morphometric techniques can be used to describe structure quantitatively and to predict mechanical gas transferring properties. Picking up the literal threads of their argument, Hoppin and Hildebrandt proceed with a superbly readable and clear account of the mechanical properties of tissue components, and then of the lung as a whole, and of the uneven stress/strain distributions within it. The home team (Pedley, Schroter and Sudlow) continue with an equally clear account of gas flow and mixing in the airways, moving easily from mathematical and physical models to real lungs. Here and elsewhere the mathematical aspects are so skillfully described that it is possible for the numerically bereft to read with enjoyment rather than despair.

The chapter by Fung and Sobin on the mechanical features of the pulmonary circulation is just as clear, though here the mathematical brambles are slightly trickier to negotiate. West and Wagner begin by summarizing Kelman's digital computer procedures, describing oxygen and carbon dioxide dissociation curves and continue with detailed programmes of their own physiological and analytical studies of V/Q distributions in real and imaginary lungs. Esther Hill and her colleagues review the kinetics of blood gas transport and so of pulmonary capillary gas exchange with particular reference to the incompleteness of carbon dioxide equillibration. Grodins and Yamashiro, in their study of control mechanisms, include the beguiling phrase that 'complex function theory is only applicable to relatively simple systems'. They also give welcome acknowledgement to Ian Priban's contributions on self-optimisation theories of respiratory control.

Because this book is clear, authoritive and small enough to read on a train, I would recommend this book to all beginning serious research on the lung. Claude Lenfant and NIH must be urged to find some way of publishing this excellent series at a cost that people, rather than institutions, can afford.

David Denison

An Atlas of Cardiology: Electrocardiograms and Chest X-rays

Neville Conway

London: Wolfe. 1977. £12

The presence of 450 electrocardiographic tracings and 300 radiographs of the heart in this atlas bears witness to the author's experience. The atlas is intended for undergraduates, family doctors and physicians, but being an atlas it is a reference book rather than a textbook.

The illustrations are excellent, although the absence of eleven from the electrocardiographic sections on myocardial ischaemia and infarction is a most unfortunate printing error. Each illustration is accompanied by an explanatory legend. Some of the rhythm disturbances could have more than one explanation but nowhere was more than one offered. For instance, the reader might well ask why some of the tracings apparently showing supraventricular complexes with observant conduction do not in fact show ventricular extrasystoles.

These points do not, however, detract from the fact that this atlas extensively covers the common cardiac conditions and also many of the less common ones.

P. J. BOURDILLON

Lung Biology in Health and Disease, 5. Respiratory Defense Mechanisms, Part II

Joseph D. Brain, Donald F. Proctor and Lynne M. Reid

New York: Marcel Dekker. 1977. Pp. xx + 498–1216. Price SFr 218

This is the second part of the fifth volume of a series of books which already have a high reputation. The first part of this fifth volume largely considered the access of particles to airways and the role of cilia, airways secretions and mucociliary clearance mechanisms. This second part takes a look at respiratory reflexes, the pulmonary lymphatics and, in particular, the role of pulmonary macrophages. The numerous contributions are of a consistently high standard and take a very thorough, detailed look at various components of the pulmonary clearance of inhaled materials and will be of particular value to anyone beginning research in this field. Much value will also be obtained by specialists from other fields of thoracic medicine who wish to learn more about this exciting new area of academic interest, although the clinician will find little of practical help to him.

As is often the case, the most successful aspect of this book contributes to its weakness. Each chapter provides a deep and detailed understanding of the subject and is, in effect, a review article. Unfortunately, a book containing a series of review articles, even if they are related to a common subject, tends to make for difficult reading and what is required in a book of this nature is a synoptic view. This could either have been provided by the editors writing linking chapters or a summary chapter at the end of the book, or by the authors of individual chapters producing a reasonable summary of their conclusions, with particular reference to the book as a whole and disease in general. Although some chapters are written for a general reader, the majority are likely to be read, with profit, mainly by those actually working in the field of the particular chapter concerned.

These comments about detail and specialization do not detract from the excellence of this volume, which can provide abundance of information both to new readers and to those who are already working in the field of respiratory defence mechanisms. It is quite clear, having read this book, that this subject is an exciting new area of activity which should pay handsome dividends to patients in the future.

T. J. H. CLARK

Respiratory Intensive Care

Robert M. Rogers

Springfield, Ill.: Charles C Thomas. 1977. Pp. xviii + 425. Price $29.50

This book is not intended as a comprehensive treatise of respiratory intensive care but rather contains a selection of articles chosen by the editor on particular subjects that have presented the most difficulty to his students.

There are 23 separate chapters, 18 of which have previously appeared in the journals *Chest* and *Postgraduate Medicine*. They cover a variety of topics, including the administration and organization of respiratory care units, acid–base balance, chronic respiratory disease, mechanical ventilation, fibreoptic bronchoscopy and extracorporeal membrane oxygenation.

Each chapter is well written and unnecessary repetition is avoided. The end-product is a book that will be of help and interest to all concerned in respiratory care, doctors, nurses and physiotherapists.

J. TINKER

Br. J. Dis. Chest (1978) 72, 347

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FUTURE MEETINGS OF THE BTA

8 December 1978 (whole day)	Royal College of Physicians, London
2–5 July 1979	Churchill College, Cambridge. Jointly with the Swedish Thoracic Society
7 December 1979 (whole day)	Royal College of Physicians, London
9–11 April 1980	University of Swansea
Autumn 1980 (date to be finalized)	Norway. Jointly with the Norwegian Thoracic Society
5 December 1980	Royal College of Physicians, London. To be confirmed
Spring 1981	To be arranged
29 June–2 July 1981	The BTA and the Chest, Heart and Stroke Association have offered to host the European region of the International Union Against Tuberculosis at Churchill College, Cambridge
30 June–3 July 1982	University of York

Further details about these meetings may be obtained from Dr J. R. Mikhail, Royal National Hospital, Bourne Avenue, Bournemouth.

FUTURE MEETINGS OF THE THORACIC SOCIETY

1–3 February 1979	Royal College of Physicians, London. Members of the American Thoracic Society have been invited to attend
6–7 June 1979	Paris. Jointly with the French Thoracic Society
7–9 February 1980 (to be confirmed)	Royal College of Physicians, London
3–4 July 1980	Durham. Members of the BTA and the Belgian Thoracic Society are particularly invited to attend this meeting; details will be circulated

Further details about these meetings may be obtained from Dr S. W. Clarke, Department of Thoracic Medicine, Royal Free Hospital, Pond Street, London NW3 2QG.

PAPERS INVITED

The British Thoracic Association invites papers for presentation at its Annual Meeting for 1979, to be held in July 1979 at Churchill College, Cambridge, jointly with the Swedish Thoracic Society. Summaries of 200–300 words should be submitted to the Honorary Secretary, Dr J. R. Mikhail, Royal National Hospital, Bourne Avenue, Bournemouth, by 31 January 1979.

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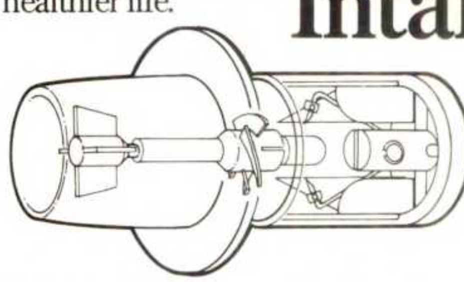

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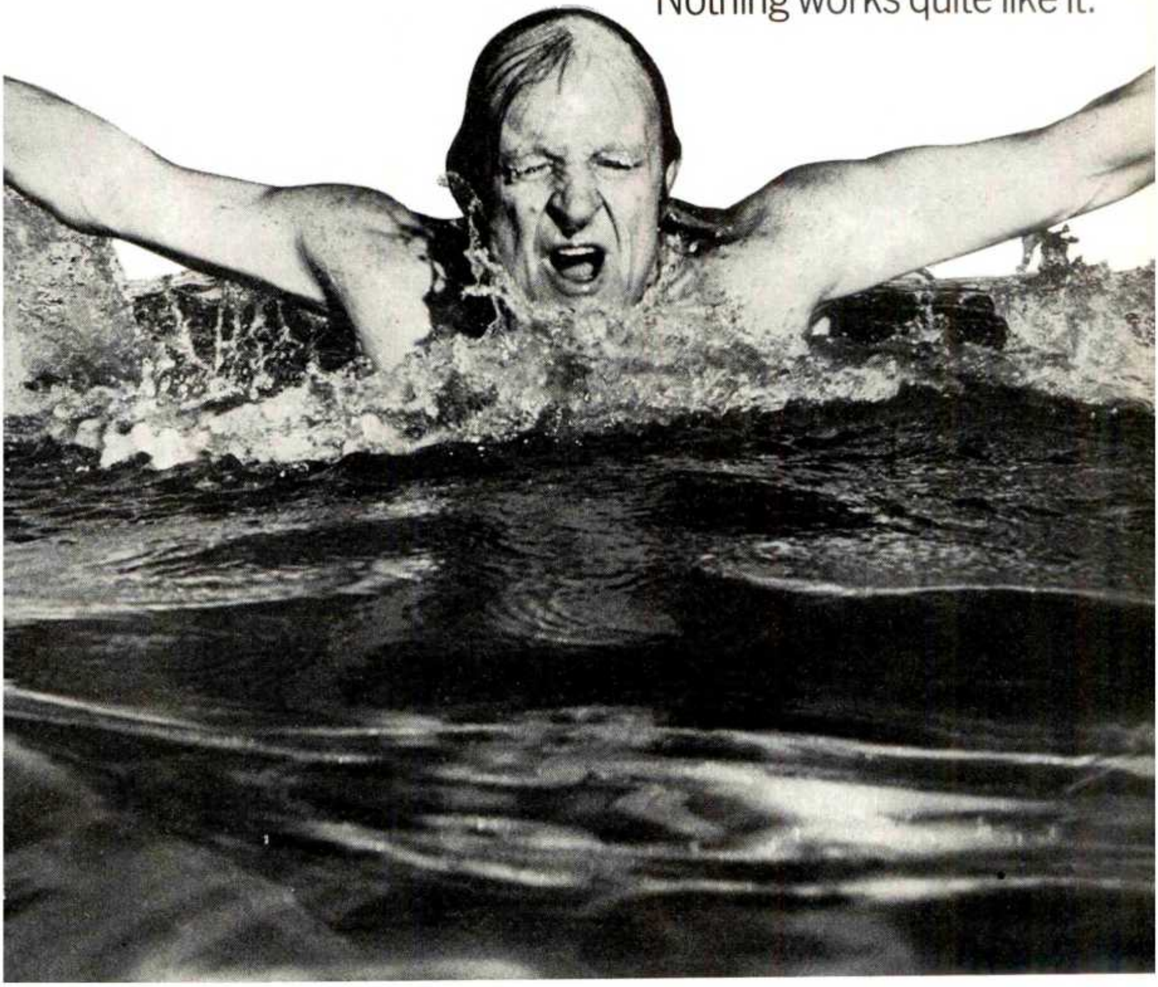

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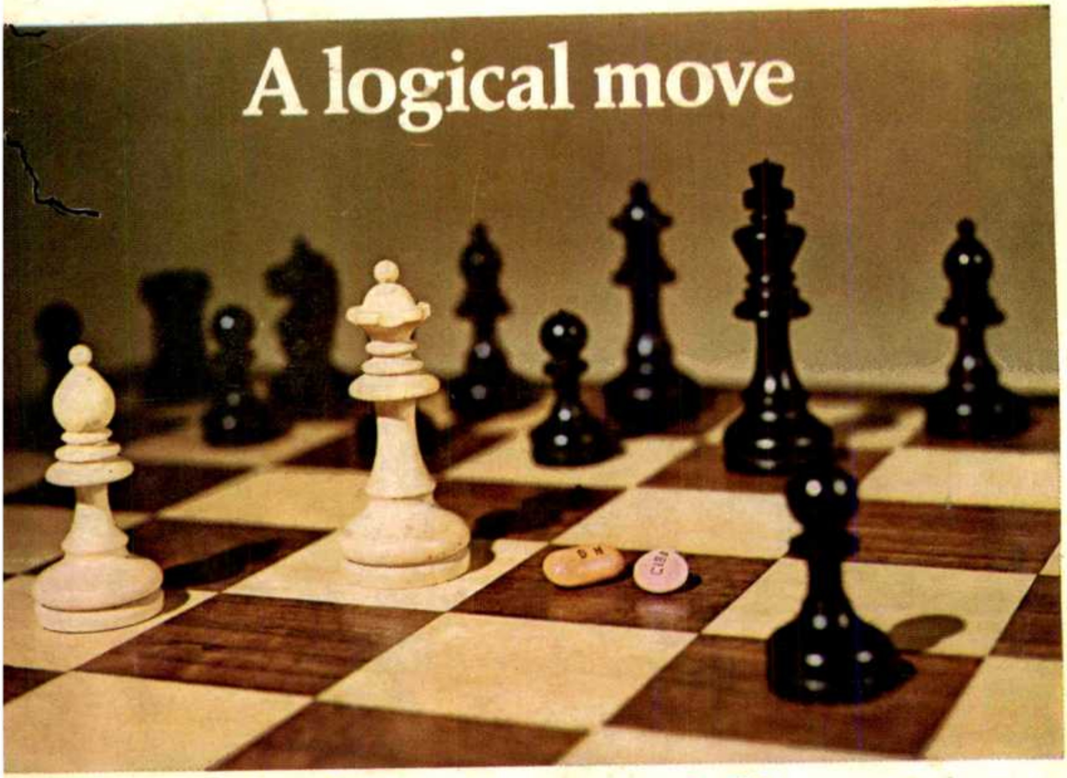

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